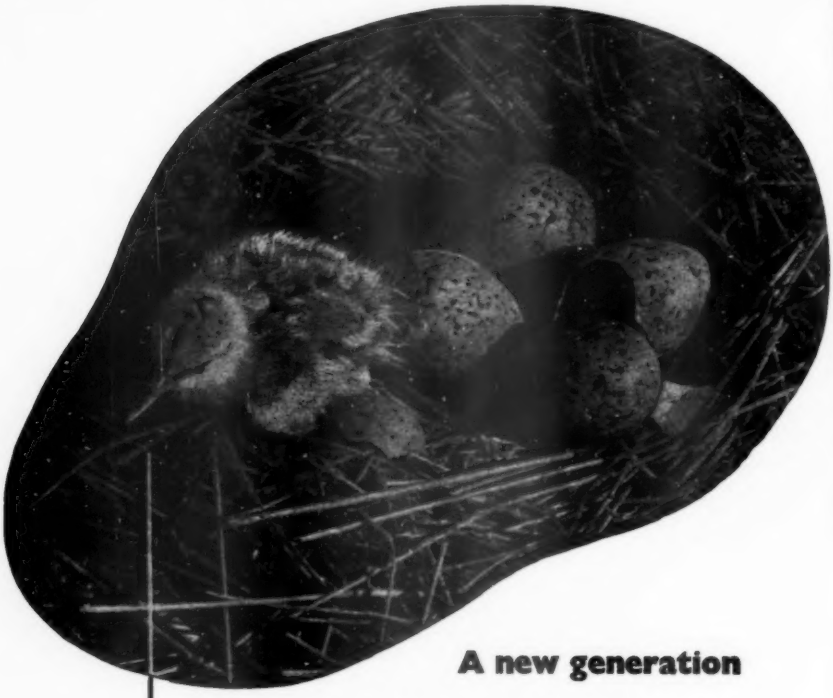
VOLUME 46 NUMBER 7 JULY 1953

PROCEEDINGS *of the* ROYAL SOCIETY OF MEDICINE

Published for
THE ROYAL SOCIETY OF MEDICINE, 1 WIMPOLE STREET, LONDON, W.1
by
H. K. LEWIS & Co. LTD., 136 GOWER STREET, LONDON, W.C.1
In U.S.A., GRUNE & STRATTON, INC., 381, FOURTH AVENUE, NEW YORK CITY
Monthly, 10s. 6d. net Annual Subscription, £6 6s. in the British Commonwealth, $19.00 in the U.S.A.



A new generation

The introduction of Chloromycetin was the beginning of a new era in the history of medicine. Its discovery and isolation in the Parke-Davis Research Laboratories and its subsequent synthesis on a large scale manufacturing basis can be counted among the really great events in chemotherapy. Moreover, the ever increasing use of Chloromycetin provides convincing evidence of the effectiveness of this latest Parke-Davis contribution to the advance of medicine.

CHLOROMYCETIN

The first synthetic antibiotic

Parke, Davis & Company, Limited *Inc. U.S.A.* Hounslow, Middlesex

Telephone Hounslow 2361

410

PROCEEDINGS *of the* ROYAL SOCIETY OF MEDICINE

ISSUED UNDER THE DIRECTION OF THE EDITORIAL COMMITTEE

All communications concerning Editorial Business should be addressed to
THE HONORARY EDITORS, 1, WIMPOLE STREET, LONDON, W.1 (Tel.: LANGHAM 2070)

PROCEEDINGS
OF THE
ROYAL SOCIETY OF MEDICINE

Vol. 46 No. 7 July 1953

CONTENTS

Continued overleaf

CONTENTS (*continued*)

N.B.—The Society does not hold itself in any way responsible for the statements made or the views put forward in the various papers.

Section of Laryngology

President—J. P. STEWART, M.D., F.R.C.S.Ed.

[*December* 5, 1952]

DISCUSSION ON THE MANAGEMENT OF INJURIES OF THE NOSE AND UPPER JAW

Mr. E. G. Collins:

The Early Treatment of Facio-maxillary Injuries [*Abstract*]

Occasionally when a patient has an extensive injury to both upper and lower jaw, tracheotomy may prove to be an emergency measure of great importance, especially in extensive gunshot wounds. To-day our attention is fortunately occupied more with civilian casualties than with gunshot wounds yet the principles which were laid down for the early treatment of wounds of the upper and lower jaw apply equally to the compound types of facio-maxillary injuries we meet to-day. These well-recognized principles are: (1) Excision of the skin edges in compound facio-maxillary injuries should be confined to devitalised tissue and no extensive debridement should be attempted. If the skin is thoroughly cleansed with soap and water or Cetavlon to get rid of dirt, most skin wounds will heal remarkably well owing to the excellent blood supply of the face.

(2) Tension on skin wounds must be avoided. Where considerable skin loss is present such as may occur with an extensive gun-shot wound involving a sinus, no attempt should be made to draw the skin edges together. In such cases it is better to suture the skin to any mucous membrane available so that the edges of the fractured bone are protected.

(3) Where there is a badly comminuted fracture involving one of the paranasal sinuses below the wound, only loose pieces of bone should be removed. Any fragment that has a chance of survival should be preserved. A small entrance wound may conceal extensive bony injury below it and a further incision in the appropriate area may have to be made to allow adequate inspection of the sinus.

(4) Drainage is important but as an emergency measure in a severe compound fracture it is better not to carry out primary suture with drainage but rather to dust the cavity with penicillin-sulphonamide powder and pack with a gauze strip wrung out in saline.

I am conscious that, as a rhinologist in one of the forward areas, I tried too much in the way of intranasal drainage in the early months. Neither the time nor the place was really suitable.

Fractures of the Nasal Bones

In a discussion before this Section in 1942, Mr. Pomfret Kilner stated that very few nose and throat surgeons were sufficiently radical in dealing with simple fractures of the nasal bones. Nowadays we realize that free disimpaction and mobilization under general anæsthesia are essential.

As Kilner pointed out, it is a useful check on the efficacy of treatment to make sure that the nose can be made to deviate readily to the side opposite to the original displacement. In the simple non-comminuted fracture no splinting is required and there is seldom any cartilaginous displacement. The severely comminuted fracture, however, presents a more serious problem. Often there is considerable swelling round the nasal bones and some delay in treatment may be both justifiable and preferable. An X-ray picture will sometimes reveal an injury to the maxilla which has not been recognized clinically owing to the swelling.

Negus (1942) drew attention to the importance of maintaining asepsis and of applying some disinfectant to the nasal vestibules. I, personally, use penicillin cream for the nasal vestibules and 1% ephedrine in saline nasal drops as a vasoconstrictor to improve the nasal drainage. The method of disimpaction with Walsham's forceps in the comminuted fracture is essentially the same as for the simple fracture but usually some form of splint is necessary. I use an underlay of Elastoplast covered by a Cellona plaster splint. The Elastoplast underlay secures closer apposition of the plaster to the nose than would otherwise be the case. Other satisfactory splints are the ribbon gauze and collodion splint of Negus and a dental stent or metal splint.

Only in the severely comminuted depressed fracture such as occurs in the "dish-face" deformity will it be necessary to retain the nose in a forward position by employing the more elaborate metal splint which is incorporated in a plaster head cap.

I find cartilaginous fractures and dislocations most difficult to deal with. Though replacement is attempted and apparently a satisfactory position has been secured, the elasticity of the cartilage reasserts itself once the restraining influence of the finger stall pack is removed. In a particularly obstinate case of fracture dislocation of the nasal septum, I obtained a satisfactory result by a loop traction suture through the cartilage with the ends tied over a roll of gauze placed above the ala nasæ on the side opposite to the displacement. Often, in fracture dislocations of the septal cartilage, subsequent submucous resection of the septum is necessary.

Facio-maxillary Injuries Involving the Paranasal Sinuses

Injuries to the Fronto-ethmoidal Area

Injuries to the lacrimal bone may cause obstruction or injury to the nasolacrimal canal resulting in epiphora. Such a sequela can usually be avoided by disimpaction and good alignment of the fragments but, occasionally, a dacryocystorhinostomy operation may prove necessary. Obstruction of the nasofrontal duct may result in a vacuum sinus type of headache. By far the most important injury to the ethmoid is fracture of the cribriform plate with accompanying cerebrospinal rhinorrhœa.

Anosmia has been mentioned as a common symptom in this type of injury but in the cases I have seen the sense of smell was seldom affected. The treatment of such cases belongs to the neurosurgeon.

I understand that there is an increased tendency to operate early on all these cases. A fascial graft is applied intradurally to the tear by an approach through a large frontal osteoplastic flap and the approach through the posterior wall of the frontal sinus has been largely abandoned even when this area is readily accessible owing to its involvement in some extensive compound injury. The argument advanced for early fascial graft repair is that, even if the cerebrospinal rhinorrhœa ceases spontaneously and the dural tear heals, the resultant scar is weak and liable to admit infection should subsequent sinusitis occur, whereas with a fascial graft the "dural seal" has proved effective even in the presence of sinus infection. This opinion received support from the figures presented by Major Calvert to this Section in 1942 which showed that the results obtained by operating on cases of cerebrospinal rhinorrhœa and intracranial aerocele were considerably better than those obtained by conservative treatment.

Frontal sinus fractures may be divided into two groups according to whether they involve the anterior or posterior walls. Simple linear fractures of the anterior wall can be left alone but, as suggested by Negus, a depressed fracture can often be levered up with a septal elevator by making an incision along the supra-orbital margin.

Where the posterior wall of the frontal sinus is involved, there is the potential danger of an accompanying dural tear and cerebrospinal rhinorrhœa may be present. Occasionally, however, a dural tear may be present without this revealing symptom and these cases form a very real problem. If the tear is unrecognized and the sinus becomes infected intracranial complications may develop, even some months after the injury. Is the neurosurgeon to operate on a case with a *possible* dural tear but no symptoms, or is he to adopt expectant treatment? Probably no firm answer can be given and each case must be considered on its merits after obtaining all the help possible from a good series of X-ray pictures of the skull.

It is, however, the severe compound comminuted fracture of the fronto-ethmoidal region involving one or both frontal sinuses with cerebrospinal rhinorrhœa that I should like to discuss. Schorstein (1944), Calvert (1942) and other Army neurosurgeons, after closure of the dural tear, have advocated complete obliteration of the frontal sinus with exenteration of the ethmoid cells and removal of all mucosa as a routine procedure even though the frontal sinus shows no evidence of infection. However, some of the neurosurgeons rather doubt that the removal of the mucosa is altogether wise, e.g. Schorstein states: "Arguments may be raised against this latter procedure and the writer confesses that he is not convinced whether it is really necessary. It is certain that one can never remove it all, equally that its removal can do no harm."

Cairns (1942) also has expressed doubt about the wisdom of this mucosal eradication.

With our experience of frontal sinus surgery we should have some useful contribution to make on this point. Personally I believe it is an extremely difficult operation to obliterate a large frontal sinus satisfactorily without leaving any pockets and I consider the attempt at eradication of mucous membrane from a sinus which shows no macroscopical evidence of infection a harmful objective, since, at best, the reformed mucosa is not comparable with normal healthy mucosa.

Our primary aim in all these frontal sinus injuries should be to prevent infection of the sinuses. Provided there is satisfactory drainage to a sinus, the chance of infection, even in a severe compound comminuted fracture of the fronto-ethmoidal region, is not great especially if strict asepsis is maintained.

In Major Calvert's series of 100 cases there were only 3 in which there was clinical evidence of frontal sinusitis in the weeks following the injury. The risk of infection is probably greater with gunshot wounds than it is with ordinary civilian casualties.

Sinus treatment in any severe compound comminuted fracture of the fronto-ethmoidal region which is not clinically infected should be limited to removal of loose and devitalized pieces of bone only, retaining any pieces that have a chance of survival. Mowlem (1941) has found that bone chips are extremely resistant to infection. If this is the case there is all the more reason to suppose that the fractured walls of the frontal sinus will survive if they can get any reasonable blood supply. If injury to the fronto-nasal duct is suspected and the compound injury does not allow free inspection of the area of the fronto-nasal duct an incision along the supra-orbital margin should be made and the floor of the sinus removed if necessary. The fronto-nasal duct is then gently explored with a small frontal sinus cannula. Should the duct prove patent nothing further will be necessary except to close the compound wound and stitch in a small-bore polythene tube. Through this, daily

instillations of 2 c.c. of crystalline penicillin solution (strength 1,000 units per c.c.) are made eight-hourly for one week at the end of which time the tube is removed. If the fronto-nasal duct is extensively damaged further removal of ethmoid cells with enlargement of the fronto-nasal duct may be necessary though the more one can retain of the mucosa of the fronto-nasal duct the better. In this type of injury intranasal drainage can be secured by employing a medium-sized rubber catheter cut short, the expanded end being placed in the most dependent part of the frontal sinus and the other end stitched to the ala nasæ. The penicillin instillation technique is again employed. If penicillin is also given parenterally for the first fortnight or three weeks after the injury the chance of any spreading osteomyelitis of the frontal bones is remote.

This conservative treatment can be performed in conjunction with the neurosurgeon after he has repaired the dural tear by a fascial graft and the following is a good illustration.

Case Report

Male, aged 45.

Whilst throwing logs on a circular saw the patient mistimed his throw and one of the heavy logs landed between his eyes. He sustained a compound comminuted fracture of both walls of the frontal sinuses, the ethmoids and nasal bones with a closed fracture of the anteromedial angle of the left maxilla. Due to rupture of the globe he had loss of sight in the right eye. He was admitted to the neurosurgical ward twenty-four hours after his accident with free leakage of cerebrospinal fluid from his frontal wound. Mr. Martin Nichols carried out a transfrontal exploration through a large osteoplastic flap. Both anterior fossæ were examined and a dural tear 1 cm. in length was found just anterior to the cribriform plate on the left side with a considerable defect of the posterior wall of the frontal sinus in this area. Both walls of both frontal sinuses were, however, extensively damaged, more so on the left side. A large piece of the left supra-orbital margin was lying loose in the sinus along with a considerable number of finer fragments from the posterior wall of the left sinus and sinus septum. The diagrammatic reconstruction (Fig. 3) gives a clearer idea of his injuries than would be visible on the X-ray plates (Figs. 1 and 2). The non-viable fragments were removed but a number of others that had some periosteal attachments were retained and moulded as far as possible into position though accurate retention was difficult owing to the great comminution.

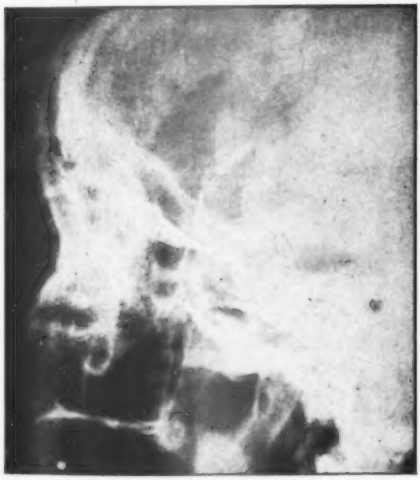


Fig. 1.—Lateral X-ray of skull before operation. Note almost complete obliteration of frontal sinuses.

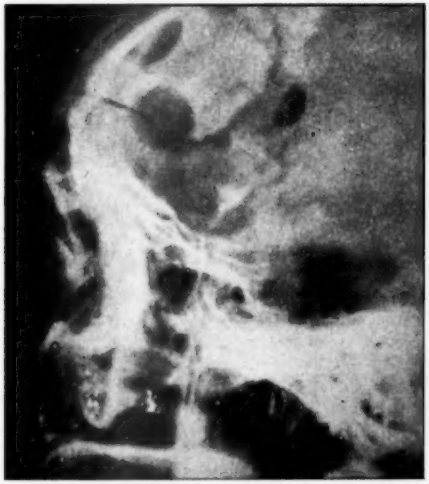


Fig. 2.—Lateral X-ray of skull after operation. Note improved aeration of frontal sinuses and lines of osteoplastic flap.

Consideration was given to the question of draining the frontal sinuses but since, after reposition of the nasal bones, it appeared that the frontonasal ducts were patent and intact, we decided to dispense with drainage in the first instance, though we realized that a re-exploration of the sinuses for the provision of drainage might be necessary should infection supervene. A plaster splint was applied to the nasal bones. The reposition of the displaced upper and inner angle of the left maxilla was delayed for ten days as we did not wish to prolong the operation. Satisfactory reduction of this fragment was secured by a Caldwell-Luc approach and the insertion of an antral pack ten days later. In this case no intranasal opening was made as the structure of the lateral nasal wall was weak.

Convalescence was uneventful and the patient was discharged from the ward twenty-three days after admission (Figs. 4 and 5). He has attended for regular follow-up since. No infection of the sinuses has occurred up to the present time. It seems to me that this would have been precisely the type of case where an obliteration operation on both frontal sinuses would have been performed if the former routine of treatment had been adopted.

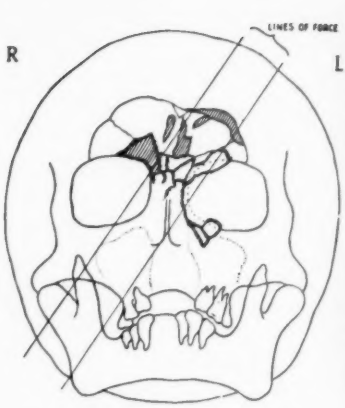


FIG. 3.—Diagrammatic reconstruction of facial injuries. Shaded areas denote completely loose pieces of bone which were removed. Dotted line indicates normal contour.

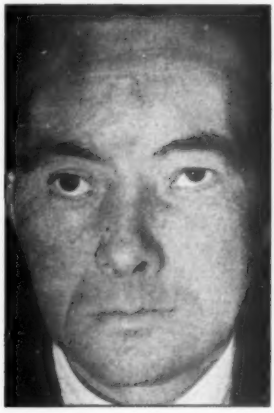


FIG. 4.

FIG. 5.

FIGS. 4 and 5.—Full face and profile photographs taken 21 days after operation.

The infected frontal sinus following a compound injury can be treated in a similar manner, provided the co-operation of the rhinologist is sought before any gross irreversible changes have occurred in the mucosa of the frontal sinus. The diagnosis of such an infection may have to be made largely on clinical grounds since the radiological appearances can be misleading. If every case of serious frontal sinus injury were handed over to the rhinologist by the neurosurgeon for regular follow-up the necessity for deforming obliteration operations on the frontal sinus would disappear.

REFERENCES

CAIRNS, H. (1942) *Proc. R. Soc. Med.*, **35**, 809.
CALVERT, C. A. (1942) *Proc. R. Soc. Med.*, **35**, 805.
KILNER, T. P. (1942) *Proc. R. Soc. Med.*, **35**, 516.
MOWLEM, R. (1941) *Brit. J. Surg.*, **29**, 182.
NEGUS, V. E. (1942) *Proc. R. Soc. Med.*, **35**, 513.
SCHORSTEIN, J. (1944) *Brit. J. Surg.*, **31**, 221.

Mr. D. S. Middleton: Having discussed the general indications for treatment continued—

Fractures of the facial bones involving the zygoma are relatively common. They are always due to direct violence and accompanied by considerable degrees of swelling of the surrounding soft tissue. The body of the bone is strong and is a buttress of protection to the contents of the orbit. It is seldom fractured itself—more usually becoming detached and displaced.

The effects of the trauma are transmitted to the bones of its attachment and the lines of fracture are in this area involving structures and presenting problems of treatment which are in the province of the ear, nose and throat and the ophthalmic surgeon (Fig. 1).

In many cases the displacement of the bone is minimal and accompanied by little deformity of the facial contour. The more severe injuries where the bone is detached and driven into the antral cavity are associated with ocular disturbances, limitation of mandibular movement, anæsthesia in the distribution of the infra-orbital branch of the fifth nerve and flattening of the facial contour.

Anatomy.—The zygomatic bone is quadrilateral in shape and has two processes: (*a*) Frontal; (*b*) Temporal. It constitutes the lateral margin, part of the floor and inferior border of the orbit. It enters into the formation of the maxillary sinus and the infratemporal fossa. The two processes articulate (1) superiorly with the frontal bone, (2) posteriorly with the arch of the temporal bone. It is attached inferiorly to the maxillary bone and internally to the sphenoid.

The mesial suture line lies slightly lateral to and above the infra-orbital foramen.

Attachments.—The masseter, temporalis and muscles of facial expression are attached to its surface and most important of all the lateral palpebral ligament, a prolongation and thickening of the septum orbitale which along with the orbital fat supports the eye (Fig. 2).

Fracture.—The commonest injury is simple fracture dislocation with separation at the fronto-zygomatic, sphenoid and temporal suture lines. The body of the bone is displaced downwards and inwards through the lateral wall of the maxillary sinus where it is usually impacted. Fractures of the arch are not so common. Mansfield (1948) in a recent review of 153 cases found that they formed

6·5% of the total number. The contour of the orbit is broken and there is a step deformity above the infra-orbital foramen.

When the trauma has been severe it may be accompanied by fracture of the body of the bone, comminution of the floor of the orbit and maxillary bone and occasionally fracture of the ethmoidal plate and nasal bones. The antral cavity subsequent to the tearing of the mucosal lining is filled with blood clot. Anæsthesia in the area of distribution of the infra-orbital nerve is almost always present. The backward and downward displacement of the bone may interfere (by impinging on the coronoid process) with mandibular movement.

The downward displacement of the lateral wall of the orbit to which is attached the palpebral ligament lowers the level of the outer canthus. The eye is no longer supported in its transverse axis, causing a vertical diplopia (Fig. 3). The diplopia may be masked on account of concussional damage to the eye itself or hæmatoma of the lids. If untreated it always persists but gradually becomes less evident to the patient who is able by cortical suppression to prevent simultaneous perception. There is, however, a loss of stereoscopic vision and ability to appreciate depth and thus, although the patient may overcome the diplopia, he has in the loss of simultaneous vision a serious handicap. Cortical suppression occurs slowly in adults and more rapidly in children as shown by the amblyopia which develops in convergent squint. The degree of comfort is, however, more readily attained after compensation is settled. *Cyclophoria* or deviation of the vertical meridian of the cornea from its normal vertical axis may occur if the attachment of the inferior oblique muscle to the lacrimal bone

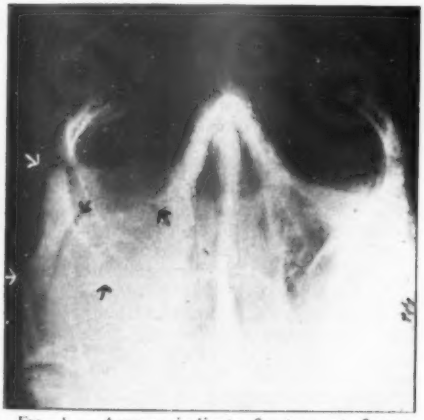


FIG. 1. — Arrows indicate fracture at fronto-zygomatic suture, lower border of orbit, lateral wall of antrum, body of zygomatic bone and temporal arch. Note also opacity of antrum due to hæmatoma.

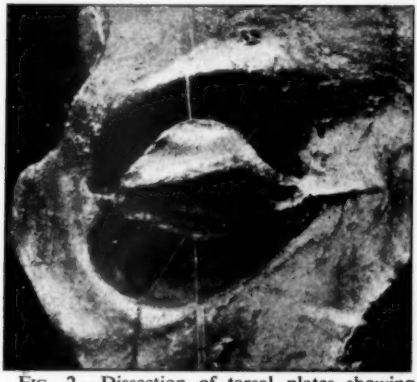


FIG. 2.—Dissection of tarsal plates showing attachment of medial and lateral palpebral ligaments. Taken from "Anatomy of the Human Orbit and Accessory Organs of Vision", by Whitnall, S. E. By kind permission of the Oxford University Press, London.

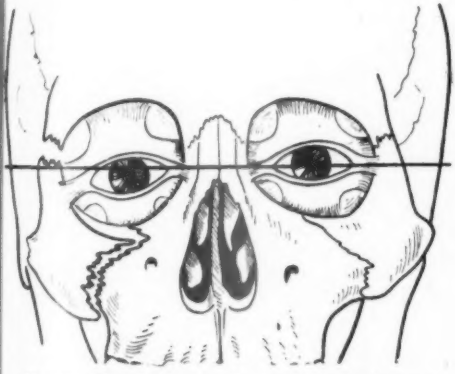


FIG. 3.—Showing lowered level of lateral palpebral ligament in cases of fracture with downward displacement of zygomatic bone.

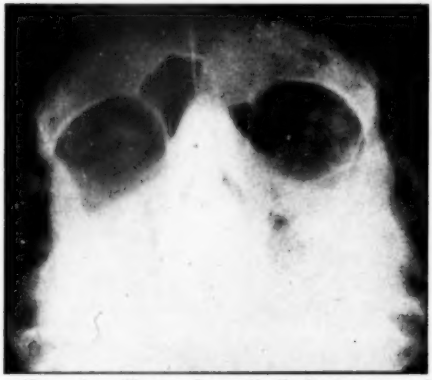


FIG. 4. — Shows inward displacement and impaction of zygomatic bone, causing some rotation of eye. Opacity of antrum.

is damaged. Intorsion of the eye results from unopposed action of the superior oblique muscle. Its presence is suspected if the patient tilts the head on viewing an object. It is one of the most difficult complications to treat and may not be corrected by lenses (Fig. 4).

Traumatic Injury

History and diagnosis.—It is important to ascertain whether there has been any (1) previous naso-antral infection, (2) discharge of cerebrospinal fluid from the nose which would indicate dural rupture.

If seen early the case presents the characteristic flattening of the cheek when viewed from behind and above. This may be masked by the subsequent swelling and œdema. A firm diagnosis on clinical examination can be made if anæsthesia of the side of nose is present and one can palpate a step deformity of the lower border of the orbit. Intra-oral examination reveals a loss of space and contour of the zygomatic maxillary arch in the buccal sulcus.

X-ray examination is essential in order to determine the extent of damage, the displacement and planning of line of treatment. An exaggerated nose-chin projection gives the best view.

Treatment is directed to restoration of function and appearance. There are a variety of methods by which the bone may be elevated and moulded into position:

Intra-oral.—If seen within forty-eight hours many of the less severe fractures may be reduced by intra-oral digital pressure under a short general anæsthetic. The bone may be heard snapping into position when the impaction is undone. In those cases where there has been a history of previous antral infection this should be supplemented by intra-nasal drainage and evacuation of the clot. Kazanjian and Converse (1949) advocate the use of a lever passed behind the bone through an incision in the muco-buccal fold; they have not observed any subsequent infection from this procedure. It is a method used by the late Sir Harold Stiles some forty years ago in Edinburgh. Patterson (1935) describes the use of straight tenaculum forceps to grasp the bone and, by traction, force it into position. This is in many cases satisfactory but is a method which is contra-indicated in the presence of comminution. It is frequently followed by considerable increase in the hæmatoma which is already present in most cases.

Organization of the fractures takes place quickly in the upper jaw and there is often some delay before they are reduced. Gillies *et al.* (1927) describe the use of an elevator passed downwards from an incision in the temporal fossa below the fascia temporalis; this is the most satisfactory method of manipulating fractures of the arch and disimpacting the malar bone.

This method whilst restoring the contour of the face and arch does not always eliminate a gap at the fronto-zygomatic suture. It is a simple procedure to supplement this by drawing the two ends of the bone together with a stainless steel wire, and thus ensuring that the lateral palpebral ligament and eye are restored to the correct level. A short vertical incision is made over the suture line, the two ends of the bone exposed and a hole drilled on each side with a fine dental burr and the wire (Brit. gauge 30) inserted (Figs. 5 and 6).

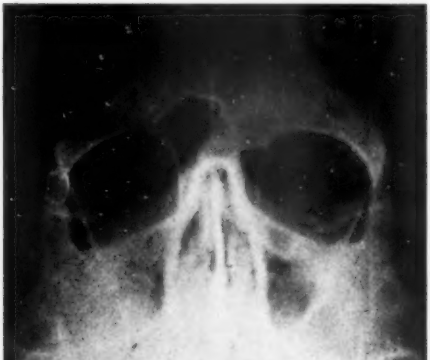


FIG. 5.—Restoration of fronto-zygomatic suture with wire ligature. Taken five days after operation. Note antrum is already beginning to clear.

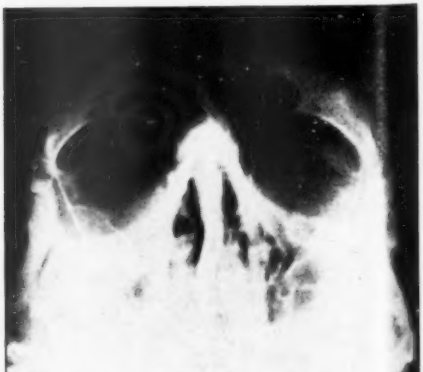


FIG. 6.—Shows use of wire sutures in cases of multiple fracture depicted in Fig. 1.

Comminution of the maxilla and floor of the orbit is an indication for direct approach through the antral cavity. I would like to make one point on the Caldwell-Luc operation. The antral mucosa, whether previously infected or not, should invariably be left intact to support the fragments. Any loose portions of bone denuded of periosteal or mucosal covering should be removed and the contour

of the cavity restored by gentle tamponage. A liberal amount of penicillin and sulphonamide powder is introduced and the replaced bones maintained in position by a pack wrung out with tinct. benzoin co. The oral incision is closed and the pack removed in seven days' time through the intra-nasal antral opening. Should that lateral nasal wall be comminuted it is often wiser to omit the making of a nasal opening and to remove the pack through the incision in the oral cavity. This may necessitate a subsequent operation to close the oral antral fistula but it allows of the fibrous consolidation of the nasal bone in the more severe injuries.

The routine use of antibiotics in simple fractures of the zygomatic bone is not indicated. The antral clot does not as a rule become infected. Indications for their administrations are (1) the presence of existing naso-antral infection and comminution of bone requiring transantral operations and (2) presence of C.S.F. in the nose indicating dural rupture.

In conclusion I would say that all cases of fracture of the zygomatic bone should have their vision checked after treatment and in the severe injury accompanied by the comminution of the orbit the opinion of the ophthalmic surgeon should be sought before any operative procedure is undertaken.

I should like to thank The Oxford University Press for their permission to use the illustration (Fig. 2) from S. E. Whitnall's "Anatomy of the Human Orbit and Accessory Organs of Vision", 2nd Ed., 1932, London, p. 151, and also Professor Sir James Learmonth and the Department of Surgery, Edinburgh, for the preparation of the other illustrations.

BIBLIOGRAPHY

AIRD, I. (1949) A Companion in Surgical Studies. Edinburgh; p. 262.
GILLIES, H. D., KILNER, T. P., and STONE, D. (1927) *Brit. J. Surg.*, **14**, 651.
ILLINGWORTH, C. F. W. (1947) Textbook of Surgical Treatment. 3rd edit. Edinburgh; p. 113.
KAZANJIAN, V. H., and CONVERSE, J. M. (1949) The Surgical Treatment of Facial Injuries. Baltimore; p. 186.
MANSFIELD, O. T. (1948) *Brit. J. plast. Surg.*, **1**, 123.
PATTERSON, R. F. (1935) *J. Bone Jt. Surg.*, **17**, 1069.

The President said that one point which he had noticed was that Mr. Collins advocated closing the wound in the upper gum margin and providing drainage of the antrum through the nose, whereas Mr. Middleton advised keeping the antral wound open and drainage into the mouth.

Mr. W. O. Lodge stressed the importance of having photographs and casts taken before operating. Anosmia or deafness should be recorded, if present. The W.R. should be ascertained, and the chest and sinuses X-rayed. It would be disconcerting to discover, late in the conduct of a case, an abnormality such as osteoma of the frontal sinus.

He had been encouraged, while working in Chicago with Cottle and Becker, to perform Joseph's section of the ascending process of the superior maxilla, using a slender keyhole saw, with a bayonet curve, and with handle bent at right-angles. The incision was made within the vestibule or in the cutaneous groove between the ala nasi and the face. A grooved director was inserted and the saw passed along the track. The section having been completed, malposition was corrected with Walsham's forceps. Sometimes elevation of the concave side sufficed, but usually it was necessary to perform a counter operation on the convex side. Dorsal humps or depressions were levelled. Subcutaneous resection of the lower lateral cartilages was performed through marginal incisions within the vestibule, the cartilages being put under tension with a fine tenaculum, and partly withdrawn. In this way, bulbous or distorted contours could be corrected.

In other traumatic cases, convoluted vomerine or maxillary fragments were laid upon a wooden block and squashed flat by a blow of the mallet; they were thus rendered suitable for reinsertion, to bring about conservative restoration. This was manifestly better practice than ruthless submucous resection.

Mr. Lodge mentioned three other points: One was that the zygomatic bone was of girder-like construction with flat surfaces which could be drilled for the attachment of stay-wires. The second was a method of wiring comminuted superior maxillæ such as would protect a suture line after an operation for cleft palate; the sutures which formed a trellis-work should not be drawn too tightly. The third item was a medico-legal episode; an insurance company paid generous compensation to a shepherd who could no longer whistle properly to his dog.

Mr. S. W. G. Hargrove showed some slides of a case in which a man had been involved in a motor-car accident. The patient had been thrown through the windscreen and he received an injury to his face and upper jaw. There was a gash involving the right orbital cavity, upper part of nose, septum, and left cheek. The injury had severed the septum and extended into the pterygopalatine fossa on each side. It was just as if the blow of a hatchet had cut his face in half. The nearest facio-maxillary unit was at Birmingham, Wordsley, and the patient was admitted to Copthorne Hospital where they dealt with emergency cases involving fractures of the upper jaw.

The patient was very ill and had to be given 4 pints of blood before operation. At operation the right eye had to be removed and it was found that there was no floor to the orbit. The eye had been

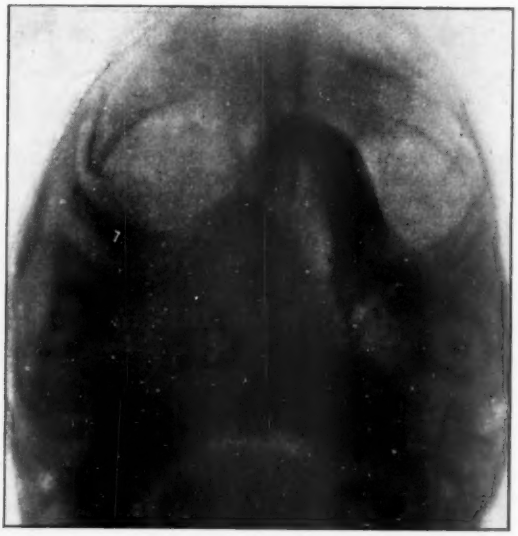


FIG. 1.—Occipito-mental view showing fracture of right orbital floor and downwards displacement of right malar bone, opaque right antrum and large gap at frontal malar suture.

FIG. 2.—Lateral view showing fragmentation of posterior edge of hard palate and downward displacement of right malar bone.

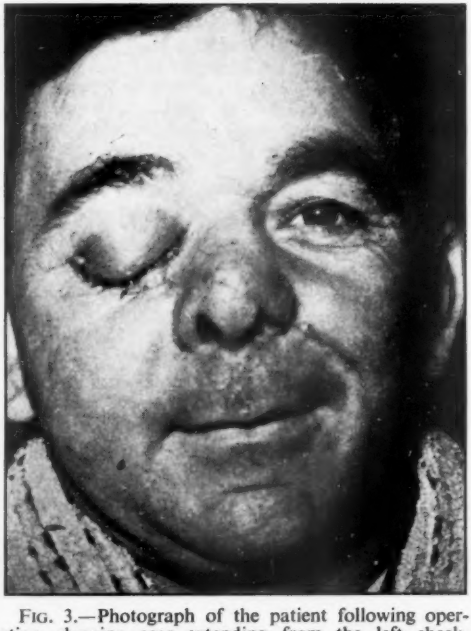


FIG. 3.—Photograph of the patient following operation showing scar extending from the left cheek, across the tip of the nose and into the right eye—there is marked œdema of the upper lid.

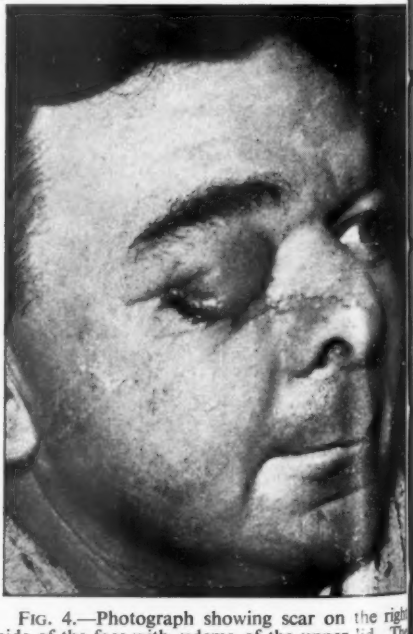


FIG. 4.—Photograph showing scar on the right side of the face with œdema of the upper lid. The patient is now wearing an artificial eye with a satisfactory eye socket.

punctured and vitreous had been lost. Mr. Hargrove found it difficult to remove the eye owing to the gross fracturing of the orbital floor. He repaired the lacerations of the lower lid and removed several small pieces of bone which were remnants of the orbital floor and then placed the remaining bones, namely the malar and the floor of the antrum and lateral side of the nose, into position. The skin edges were sewn together.

He dealt with numerous middle face fractures in his area and had not had to use the complicated splints used by facio-maxillary units as he found that these fractures healed very quickly without deformity after bringing the fractured bones in apposition by an external approach. His Dental Surgeon colleague attended to the teeth, making sure that the patient's teeth were in correct apposition using the lower jaw.

Radiologist's report (Dr. Humphrey Foy): *Facial region.*—There is extensive comminution of the right orbital floor, the right antrum, and the right ethmoidal region of the face. The right malar bone is extremely mobile, and is displaced downwards and rotated outwards, and resulting in a large gap at the fronto-malar suture.

There is a step fracture visible on the floor of the left orbital near its junction with the lateral orbital wall.

In addition, there is some fragmentation of the posterior edge of the hard palate.

The nasal bones are intact. There is a large amount of hæmorrhagic effusion in the ethmoidal malar region.

[*February* 6, 1953]

DISCUSSION ON THE MANAGEMENT OF CERVICAL METASTASES FROM LARYNGEAL CARCINOMA

Mr. Roland S. Lewis (E.N.T. Surgeon to King's College Hospital and Mount Vernon Hospital and Radium Institute): Nowadays more and more attention is being paid to the secondary deposits in the cervical lymph nodes which may arise from carcinoma of the larynx. I have always been interested in this subject because I have had more trouble with recurrence in the lymph nodes after laryngectomy than with local recurrence.

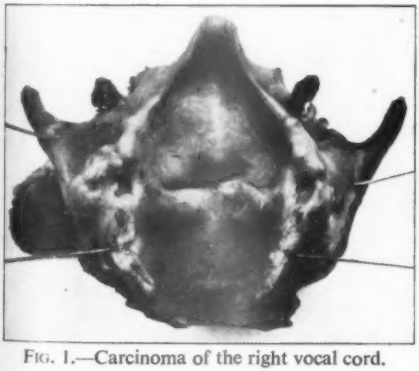


FIG. 1.—Carcinoma of the right vocal cord.

For example, Fig. 1 shows a larynx which I removed two and a half years ago. The growth was fixed and involved the greater part of the vocal fold; the ventricle of the larynx was not involved and there was very little subglottic extension—the photograph rather exaggerates this. One year later a small lymph node became palpable deep to the sternomastoid on the same side. I treated this by a radical neck dissection. Microscopic examination showed that the node had been invaded by a squamous-cell carcinoma. It is now two and a half years after laryngectomy and one and a half years after the neck dissection and the patient is alive and well—but one cannot always count on such results. Another case with a similar primary growth on the vocal cord got a recurrence in the lymph nodes four months after laryngectomy. After a radical neck dissection nodes appeared on the opposite side of the neck and though these were treated in the same way the patient eventually died of his disease.

In spite of these experiences, I believe it is exceptional to get secondary gland involvement in this type of case and I would like to make it quite clear that I do not advocate the so-called prophylactic block dissection of the neck for growths of the vocal cords. However, there are other types of growth where it might be necessary.

There has not been a great deal written on this subject in this country, though in 1952 (*Proc. R. Soc. Med.*, **45**, 255), in the Discussion at this Section on pharyngo-laryngectomy, Mr. R. D. Owen and Mr. R. Raven both recommended a block dissection of the neck at the same time as laryngectomy for growths of the pyriform fossa and hypopharynx. The subject has been considered more fully in other countries—for instance by Brachetto-Brian and Samengo (1950) and Del Sel and Agra (1947) in the Argentine and Pricolo (1950) and Bocca (1952) in Italy: in the United States Ogura and Bello (1952) advocated one-stage laryngectomy and block dissection in all cases of laryngeal cancer except the purely cordal ones. Leroy Schall (1951) and Louis Clerf (1951) have both expressed their agreement with this principle and Clerf has reported some results.

In this contribution I shall try to assess the frequency with which secondary deposits occur in the cervical lymph nodes in a squamous-cell carcinoma of the larynx, and also try to determine how often bilateral and distant metastases occur. Other types of malignant disease are rare and will not be considered.

Distant metastases.—I have met with very few distant metastases, whether in glands or viscera, and it seems generally agreed that they are uncommon and only appear late in the course of the disease. The figures given vary between 2% and 6%. Most authors merely record that metastases to the lung, mediastinum and brain may occur. The possibility of a distant deposit need not, therefore, influence one in deciding on the treatment of the primary lesion.

Cervical lymph nodes.—Secondary involvement of these structures may occur in both intrinsic and extrinsic carcinoma of the larynx. These groups were proposed by Krishaber in 1879, and in the intrinsic group (according to StClair Thomson and Negus, 1937) he included growths arising from the cords, ventricles, ventricular bands, interarytenoid area and subglottic region. The extrinsic group contained the epiglottic, aryepiglottic fold, pyriform fossa involving the larynx and post-cricoid growths. He made this grouping because cancer arising in the interior of the larynx was said to be slow in growth and relatively benign in character, and only invaded the glands at a late stage of the disease. Growths arising from the extrinsic areas are more malignant and they spread to glands early.

This grouping held the field for many years and it is still often used; it appears in the textbooks published in the 1930s—StClair Thomson and Colledge (1930), StClair Thomson and Negus (1937), Jackson and Jackson (1939), Ballenger and Ballenger (1937) and so on. But recently many writers have changed their outlook and the intrinsic area is now often very much restricted. For instance, writing in 1945, Jackson and Jackson limit the intrinsic area to the vocal cord, the ventricle and the undersurface of the ventricular band. The 1947 edition of the textbook by Imperatori and Burman defines the intrinsic area as the true cords and subglottis and Walsh (1947) even omits the subglottic area from his classification. Negus (1953) still keeps the original definition, but he considers that supraglottic and subglottic tumours should be placed in special subgroups of intrinsic growths.

It seems to me that this limitation of the so-called intrinsic area is due to the fact that it is becoming recognized that growths arising from the interior of the larynx, other than true cordal growths, can give rise to deposits in the cervical lymph nodes at a comparatively early stage of their evolution. The proposed limitations, however, do not go far enough in most cases. It is probable that the freedom of the true cordal growth from metastatic spread is, at least in part, due to the poor lymphatic network on the cord, and, if this is so, it is illogical to include with it the ventricles and the undersurface of the ventricular bands which have a rich mucosal lymphatic network. The subglottic area, also, has a much better lymphatic system than the vocal cord and it should always be considered separately.

This contribution is based on the study of recent reports and on 118 cases which I have personally observed, mostly in consultation with my radiotherapy colleagues at Mount Vernon Hospital. These cases were seen during the period 1946–1952. The period is recent and short; the number of regional node metastases, therefore, is not final and the percentage of these recurrences may yet increase.

I shall stick to the historical division of laryngeal cancer into intrinsic and extrinsic forms because it is so well known but to make things more clear I have subdivided the two groups (Table I). The

TABLE I

Extrinsic carcinoma	Intrinsic carcinoma
(*a*) Epiglottis (suprahyoid portion)	(*a*) Glottic { Mobile cord / Fixed cord
(*b*) Aryepiglottic fold	(*b*) Supraglottic (including cordal with supraglottic extension)
(*c*) Pyriform fossa (involving larynx)	(*c*) Subglottic
(*d*) Post-cricoid carcinoma	(*d*) Recurrent carcinoma
(*e*) Recurrent carcinoma	

post-cricoid growths have been put in for the sake of completeness, but I shall not discuss them. By glottic growths I mean growths still confined to the vocal fold. The supraglottic group is comprised of cases arising in the ventricles or the ventricular bands and on the laryngeal surface of the subhyoid portion of the epiglottis. I have also put into this group glottic cancers which have extended into the ventricles or on to the ventricular bands because by doing this they have left an area which is poorly supplied by lymphatics and have invaded one with a rich supply. When this happens, their degree of malignancy often increases, the cells becoming less differentiated (Jackson and Jackson, 1939). The point of origin of the growth seems to me to be of less importance than its present extension.

Extrinsic carcinoma.—I think it is generally agreed that these growths metastasize to the lymph nodes of the neck more often than not, and that this frequently occurs at a very early stage in the evolution of the growth. Indeed, the presence of a lump in the neck is often the first sign that anything is wrong and in many cases palliative treatment is all that is possible.

I have 57 cases in this group and Table II shows that in all sites there is a high percentage of lymph-node involvement—unilateral, bilateral and late. Few cases escape developing metastases.

It is mainly because of metastases that these growths are so seldom curable and if any treatment is to be effective it must pay as much attention to eradicating the lymphatic areas as to removing or

TABLE II

	Total No. of cases	Unilateral nodes when first seen	Bilateral nodes when first seen	Nodes appearing after control of primary
Epiglottis (suprahyoid)	15	6	4	2
Aryepiglottic fold	17	10	4	1
Pyriform fossa	25	13	4	5

destroying the primary growth itself. This means that, in every case of extrinsic carcinoma of the larynx that is operated upon, a radical neck dissection should be carried out, whether lymph nodes are palpable or not.

Unfortunately, these cases are, as a rule, seen so late that very few are in an operable state. It is not uncommon either to find bilateral involvement of the lymph nodes. When this occurs, or when it is suspected, one must be prepared to do a bilateral radical neck dissection. It has been claimed that it is safe to do both sides at one sitting, including removal of the jugular veins; but it is preferable to leave an interval of about three weeks before operating on the second side.

Intrinsic carcinoma.—Here we find differing opinions as to the frequency of cervical metastases. This is because the group is made up of growths arising from several different anatomical sites, and the frequency of metastatic spread from each of these sites varies. Other factors to be taken into consideration are the stage which the disease has reached and its grading according to Broder's classification. An ideal classification would include all these factors, but in practice it results in so many small groups that they have no statistical value. Many compromises have been suggested, but I will not deal with them in this paper.

The reports of recurrences in the cervical lymph nodes, which I have been able to trace in the literature, have been in the main related to their appearance after laryngectomy. For instance, Cody (1949) surveyed over 4,000 reported cases of carcinoma of the larynx. Of the cases subjected to laryngectomy, 30% developed post-operative cervical metastases without any *pre-operative* indication of their presence. The deposits must have been there at the time of the original operation because there was *no local recurrence*. It is clear that the majority of his cases were intrinsic carcinomas.

Table III gives some figures illustrating the incidence of cervical metastases in intrinsic carcinoma of the larynx as reported by various authors.

TABLE III

Author	Type and No. of cases	Palpable lymph nodes	Treatment	Actual No. with node involvement
Ogura and Bello, 1952	Intrinsic (endolaryngeal) 15	None	Laryngectomy and block dissection	6 = 40%
Tucker, 1949	Intrinsic 198	None	Laryngofissure (117) Laryngectomy (81)	5 = 2½%
Clerf *et al.*, 1948	Endolaryngeal 176	None	Laryngectomy	41 = 24·4%
Jackson *et al.*, 1948	All groups except pyriform fossa 35	None	Laryngectomy	8 = 22·8%
Negus, 1947	Intrinsic 22	None	Laryngectomy	5 = 22·8%
Blady, 1947	Intrinsic 143	None	Irradiation or laryngectomy	16 = 11%

The small percentage reported by Tucker (1949) is largely due to the fact that most of his cases were early ones. Blady's series (1947) also probably included a number of early cases.

Negus in his laryngectomies usually does a wide excision and clears the fascia of the carotid sheath on the worse side.

In addition to these cases, Clerf (1951) reported 27 cases of extensive carcinoma limited to the larynx without clinical metastases, which he treated by prophylactic block dissection and laryngectomy. In 8 of these cases (30%) cancer cells were found.

We cannot draw any firm conclusions from these selected cases since authors differ a great deal in their criteria for choosing cases for laryngectomy or other forms of treatment.

A more helpful set of figures (Table IV) was given to me by Dr. Bocca, of Milan, in 1952. They have not been published and as yet they are only approximate—the final figures are to be reported soon.

Marginal carcinoma means those growths arising from the aryepiglottic folds and free parts of the epiglottis. Groups 3 and 4 are roughly equivalent to my supraglottic group and in 30% of these cases the involvement was revealed only on section of the nodes removed at operation. Dr. Bocca concludes that a radical neck dissection, frequently bilateral, should be a part of every laryngectomy operation.

My own figures are not large enough to express as percentages—to do so might give them false importance. In this group there are 61 cases of squamous-cell carcinoma (Table V).

TABLE IV

Site of primary growth	Percentage of positive nodes
(1) Pyriform fossa ..	76%
(2) Marginal carcinoma	45%
(3) Ventricular band ..	50%
(4) Ventricle	35%
(5) Cordal	0·4%
(6) Subglottic	30–35%

TABLE V.—INTRINSIC CARCINOMA OF THE LARYNX

	No. of cases	Positive nodes when first seen	Nodes appearing after control of primary growth
Glottic { mobile ..	16	0	0
Glottic { fixed ..	10	0	2
Supraglottic ..	19	5	4
Subglottic ..	10	1	0
Recurrence in larynx	6	0	2

These figures, taken into consideration with other reports, support the contention that when a glottic growth has extended beyond its tissue of origin into the supraglottic region, or when it arises from the supraglottic region *de novo*, there is a considerable chance of cervical metastases being present, even though they are *not* detectable clinically. This is important because I believe that supraglottic cases are commoner than is usually supposed. Of 254 cases of endolaryngeal carcinomata reported by Lederman (1952), 64, or 25%, arose in the supraglottic portion of the larynx. Leroux-Robert (1948) has found that supraglottic cases are even more numerous (about 50%), while in the Argentine the proportion of supraglottic to glottic cases is said to be 9 : 1.

There was only one case of bilateral glandular involvement in this series.

Conclusions.—The likelihood of the lymph nodes of the neck being involved is high in certain types of cancer of the larynx, although they may not be clinically detectable. In order to deal with this possibility, it is advisable in extrinsic carcinoma of the larynx to do a full radical neck dissection, whenever operation is indicated, whether it be laryngectomy or lateral pharyngotomy. I would also do the dissection in advanced supraglottic growths, including glottic growths which have extended supraglottically. It is, of course, done only if the patient is fit enough to stand the extra procedure; though it is surprising how little it adds to the shock of operation or to post-operative disability.

We are doubtful about the necessity for prophylactic dissection in subglottic growths. Some authors recommend it, but, in our series of 10 cases of laryngectomy in this group, lymph nodes were present in only one, and, so far, none have appeared in the remaining cases.

I have not discussed the treatment of the primary growth, but I want to conclude by emphasizing that it is important to excise the larynx widely. I always remove the hyoid bone and often half the thyroid gland. In subglottic growths three, or even four, rings of the trachea are taken.

REFERENCES

BALLENGER, W. L., and BALLENGER, H. C. (1937) Diseases of the Nose, Throat and Ear. London.
BLADY, J. V. (1947) *Amer. J. Roentgenol.*, **58**, 331.
BRACHETTO-BRIAN, D., and SAMENGO, L. A. (1950) *Prensa méd. argent.*, **37**, 3033.
BOCCA, E. (1952) Personal Communication.
CLERF, L. H. (1951) *Trans. Amer. Acad. Ophthal. Oto-laryng.*, **56**, 807.
——, PUTNEY, F. J., and O'KEEFE, J. J. (1948) *Laryngoscope, St. Louis*, **58**, 632.
CODY, C. C. (1949) *Laryngoscope, St. Louis*, **59**, 621.
DEL SEL, J., and AGRA, A. (1947) *Trans. Amer. Acad. Ophthal. Oto-laryng.*, **52**, 653.
IMPERATORI, C. J., and BURMAN, H. J. (1947) Diseases of the Nose and Throat. 3rd edit. Philadelphia.
JACKSON, C. L., BLADY, J. V., NORRIS, C. M., and MALONEY, W. H. (1948) *J. Amer. med. Ass.*, **138**, 1080.
JACKSON, C., and JACKSON, C. L. (1939) Cancer of the Larynx. Philadelphia.
——, —— (1945) Diseases of the Nose, Throat and Ear. Philadelphia.
KRISHABER (1879) *Gaz. hebd. Méd. Chir.*, **16**, 518.
LEDERMAN, M. (1952) *Brit. J. Radiol.*, **25**, 462.
LEROUX-ROBERT, J. (1948) *Acta chir. belg.*, **47**, 46.
NEGUS, V. E. (1947) *Proc. R. Soc. Med.*, **40**, 11.
—— (1953) Personal communication.
OGURA, J. H., and BELLO, J. A. (1952) *Laryngoscope, St. Louis*, **62**, 1.
OWEN, R. D. (1952) *Proc. R. Soc. Med.*, **45**, 255.
PRICOLO, V. (1950) *Tumori*, **24**, 157.
RAVEN, R. W. (1952) *Proc. R. Soc. Med.*, **45**, 264.
SCHALL, L. (1951) *Trans. Amer. Acad. Ophthal. Oto-laryng.*, **56**, 806.
THOMSON, STC., and COLLEDGE, L. (1930) Cancer of the Larynx. London.
——, and NEGUS, V. E. (1937) Diseases of the Nose and Throat. London.
TUCKER, G. (1949) *Proceedings of the 4th International Congress of Otolaryngology, London*, **1**, 30.
WALSH, T. E. (1947) *Laryngoscope, St. Louis*, **57**, 414.

Mr. A. J. Durden Smith: Carcinoma of the larynx has much in common with cancer in other parts of the upper air passages, with which I am more familiar, and I believe that surgery has an important part to play in the management of the cervical metastases which are so common in this disease—a part which is not, perhaps, as widely recognized as it should be. It would seem that there is a tendency, among both laryngologists and radiotherapists, to treat the primary lesion by one means or another, and to allow the results to stand or fall by that treatment, without perhaps enough consideration of those secondary cervical events which may—and often do—place their patients in jeopardy, despite the fact that they have every reason to believe that the primary disease has been adequately controlled. I must say, at once, that my personal experience of the surgical treatment of secondary cervical glands, in so far as they relate particularly to laryngeal cancer, is limited—and that largely for the reason that my laryngological colleague manages his own metastases! The problem, however, differs only in degree from that confronting us in the treatment of cancer of the buccal cavity; and there are main general principles which apply to both; the glandular drainage area, allowing for differences in distribution, is the same, as are the hazards of clinical assessment, the standards of operability, and the details of surgical technique. Encouraging features of the glandular area are its well-defined and limited extent, and its ready accessibility. It is unusual for metastases to spread outside the area covered by the block dissection operation. As Crile pointed out forty-five years ago, it differs markedly from the lymphatic areas in, for instance, breast or stomach cancers where spread is less predictable, and often surgically unapproachable at an early stage in the primary disease. Another encouraging factor about carcinoma of the larynx is the low incidence of visceral metastases. This is admittedly higher than in the case of mouth cancers where it is probably not more than 1 or 2%, but 5% is probably a reasonable figure. In a series of 181 cases treated at Mount Vernon Hospital it was 6%, and they all appeared late in the disease; such a figure is low enough to be ignored for practical purposes when considering treatment and results in the case of cervical metastases.

Mr. Lewis has dealt in some detail with the incidence of cervical metastases in laryngeal carcinoma in the case of various primary sites. Perhaps the most important figure is that of supraglottic cancers, many of which are capable of primary cure, but which give rise to secondary glands in a large proportion of cases. Baclesse gives 40%, and Lederman the same figure. There is some difficulty in assessing their incidence in the various types of primary lesion, and there is real need of some primary classification to which all workers could subscribe. It might then be possible, for instance, to discover whether particular primary sites give rise to secondary glands in particular gland groups, and this might have a bearing on treatment, particularly as between radiation and surgery. At present we have little information to help us, although experience with cancers of the mouth suggests that to predict the probable site of gland involvement is uncertain and therefore unsafe.

Taylor and Nathanson, in a review of 89 cases of carcinoma of the larynx, gave these figures of incidence in the various groups—secondary to a wide variety of laryngeal cancers (Table I). The list

TABLE I.—CARCINOMA OF LARYNX. DISTRIBUTION OF CERVICAL METASTASES 89 CASES

Submental	4	Bifurcation	74
Submaxillary	18	Supraclavicular	22
Subdigastric } Subparotid }	52	Posterior	3

includes cases in which more than one group was involved. It is apparent from them and other figures that the distribution of glandular metastases is a wide one, that the bifurcation and subdigastric nodes are most commonly involved, but that other situations are by no means rare. It is generally agreed that surgical extirpation of the glandular area is the method of choice in cases of buccal carcinoma where operable glands exist. Radiation methods, although they sometimes effect a cure, are less certain, and are handicapped by the difficulty of delivering an adequate dose to such a large block of tissue. It would seem logical, therefore, to adopt the same principles of treatment in carcinoma of the larynx. If radical surgery of the neck is to be the method used, the primary lesion must be accounted capable of cure by the means adopted in its treatment. If the primary disease is to be extirpated by laryngectomy there is, I think, a strong case for block dissection undertaken at the same time: the principles governing the surgical removal of malignant disease do, after all, demand the continuous removal of primary lesion and lymphatic area in one piece if this is possible—as in the breast, the stomach, the rectum or the uterus. I doubt, however, whether this is as essential as it sounds. Such a procedure is not, for instance, possible or desirable in the modern radiosurgical treatment of buccal cancer. Yet it is not found that recurrence is common in the junctional tissues, where one would expect the danger to lurk. If, therefore, laryngectomy followed by block dissection of the neck—or vice versa—at the same operative session is easier than the removal of the large mass of carcinomatous tissue in one piece, there is, I think, nothing to be said against it. Indeed block dissection after laryngectomy, as long as it is done within a short time—not more than ten to fourteen days later—would seem to differ not at all from the accepted practice in cases of squamous carcinoma in other sites for which block dissection is done. If the

patient's condition makes it unwise to proceed with the neck operation at the same session, this should not preclude its being done a short time later. As regards modified operations on the glandular area, I think there is nothing to recommend them. Where one gland group is involved, the likelihood of extension to a neighbouring group is high; neither is the case for dissecting the upper half of the neck a good one, if only for the reason that the dissection of the lower half is comparatively easy and is quickly done. The operation itself involves meticulous dissection, and takes from two to two and a half hours, depending on the anatomical conformation of the neck.

Hazards.—These are few and involve for the most part damage to nerves. The superior laryngeal nerve, if damaged, results in inability to tense the affected cord, and this has a serious effect on the voice. Damage to the hypoglossal nerve gives rise to palsy of the muscles of the tongue on the side affected. This almost always recovers unless, of course, the nerve has been divided—unlikely because of its size. The phrenic nerve may be damaged or even divided. It is possible to injure the thoracic duct and its counterpart on the opposite side.

Mortality.—The high mortality figures sometimes quoted are usually found to be out of date. With modern methods of anæsthesia, the use of blood transfusion and antibiotics, mortality is small.

Disabilities.—There are two: (1) Inability to raise the affected arm higher than shoulder level due to removal of the spinal accessory nerve. (2) Palsy of the depressor anguli oris due to removal of the cervical branch of the facial nerve.

In a series of 113 cases of block dissection at Mount Vernon Hospital there were 5 post-operative deaths—a mortality of 4·4%. Permanent disability of a serious kind occurred in one patient whose superior laryngeal nerve was injured and presumably divided. There were 3 cases of hypoglossal palsy, 1 of which remained permanent. The phrenic nerve suffered in 2 patients with no marked disability. There was 1 case in which the thoracic duct was injured with subsequent lymph leakage.

No definite conclusions can be drawn from such a series because they do not apply particularly to the larynx and because the behaviour of the primary lesion is so often the deciding factor in survival. It may, however, give some idea of the protection afforded to patients with already existing malignant glands if I quote the following figures: 29 of these patients are alive and without disease for five years and 42 for three years. Of these 42, 21—exactly half—had positive glands; not all of these were diagnosed clinically as being positive, and the clinical error in this series was 9%. There seemed little difference in survival as between those who had histologically proved glands when first seen and those which arrived as Stage I cases and developed positive glands later, the numbers being 10 and 11 respectively.

Is it possible to suggest some sort of policy in the treatment of the neck in carcinoma of the larynx; Firstly for the case which is submitted to laryngectomy as a first measure, and secondly for the case in which the primary disease is treated by radiotherapy? It is far from easy, and many factors have to be taken into account. The case which has operable glands when first seen and is submitted to laryngectomy is, I think, simple. There is little doubt that block dissection of the neck offers the patient the best chance, and such a block dissection should ideally be done at the same time as the removal of the larynx. The same attitude should be adopted in those cases where glands are not palpable, but where the primary disease has a high incidence of metastases. The clinical error appears to be higher in the case of cervical glands secondary to laryngeal cancer than in those arising from other primary sites. The operation adds little to the risk of the operation for the primary cancer as Mr. Lewis has shown; and a second operation is avoided. There is also that group of cases who develop inoperable glands between one follow-up visit and the next.

More difficult is the case in which radiation therapy is given for the primary disease. Since it is true that the first gland group to be involved is commonly in the bifurcation or subdigastric region and can be included in the teleradium or X-ray beam, it would seem reasonable in the absence of palpable glands to treat the case in this way, delivering a lethal dose to this limited glandular area, and await events. When glands are palpable the problem becomes a difficult one for the likelihood of wider spread is real, and treatment of the primary disease by radiation methods takes time, resulting in delay which may be dangerous. There is little to be said for block dissection before radiation therapy from any point of view—it has intrinsic disadvantages and creates difficulties for the radiotherapist. There may occasionally be a case here for treating with radiation and being prepared to do a block dissection at the appropriate time after treatment has finished, if necessary. Above all, if the expectant method is adopted in the absence of palpable glands, the follow-up must be careful and the interval between visits of the patient not more than a month apart so that if glands become involved, he may have the benefit of immediate block dissection.

In the light of our present knowledge the following is a reasonable policy to adopt in these cases.

In cancer of the larynx in which the incidence of glandular metastases is high, and in which the primary lesion is regarded as possible of cure:

Surgical Treatment of Primary Lesion

(1) No palpable glands
(2) With palpable glands } Laryngectomy and block dissection.

Radiotherapy of Primary Lesion

(1) No palpable glands (2) With palpable glands	Careful follow-up after treatment. Block dissection if glands appear. If the gland, especially if small, is well within the radiation field, watch the case, and interfere by block dissection if necessary. But there is a case here for treating the disease by laryngectomy with block dissection.

The adoption of a common classification of the primary disease is of vital importance. More information is wanted about the actual cause of death in unsuccessful cases—particularly whether it is due to uncontrolled primary disease or to metastatic events or to both. It would be helpful, too, to have more exact knowledge as to whether the site of glandular invasion has any relation to the site of the primary disease—knowledge of it might have an important effect on choice of treatment. Such factors would have an important bearing on policy in treatment and would focus attention on the significant part which secondary cervical disease plays in the high mortality of laryngeal cancer.

Dr. G. Picciotto: The problem of gland metastases from carcinoma of the larynx looms large in the management of this condition. The highest incidence is found in the tumours originating from the ventricles or ventricular bands which have spread to the epiglottis or aryepiglottic fold, and in those which cover the same area but have spread from above downwards. Carcinomas arising in the pyriform fossæ are also great offenders in this respect. The treatment of these metastases cannot be considered apart from that of the primary tumours.

That block dissection is the best procedure for operable metastatic glands and radiotherapy the only practicable one for inoperable glands is a long-standing commonplace which clearly points to the right treatment in the appropriate case.

There is, however, an important group of patients in whom no glands are palpable. Radiotherapy and surgery in the form of laryngectomy or pharyngo-laryngectomy are the two methods of treatment at our disposal: they complement each other. Radiotherapy has made a contribution in this field by combining cure with a large measure of preservation of function, not discounting its small late morbidity. The indications for surgery are not always clear cut, but involvement of cartilage, excluding the elastic cartilage of the epiglottis, and recurrence after radiotherapy are two of them. Generally speaking, although this needs defining in practice, the extensive growths are more amenable to surgery.

A proportion of patients in this group are at risk for they harbour microscopic deposits of growth in their lymph nodes which will grow to become palpable after the successful treatment of a laryngeal tumour by either method. When radiotherapy is used for the primary tumour, the present practice is to keep the patients under observation and resort to block dissection of the neck should this prove to be necessary.

The necessity for a careful follow-up is obvious. The purpose of this communication is to put forward some evidence to show that radiotherapy has a useful part in the treatment of patients suffering from inoperable metastatic glands.

Fig. 1 is from a biopsy of a well-differentiated squamous-cell carcinoma of the upper part of the œsophagus; it shows well-defined clumps of neoplastic cells with abundant keratin formation. The nuclei and outlines of the cells can be made out against the background of keratin. The intervening stroma is the site of an inflammatory reaction.

Fig. 2 is from a section of a gland in the same patient six weeks after irradiation; it shows a mass of keratinized debris; the tumour cells have vanished, leaving behind scattered nuclei; there is also a foreign body giant-cell reaction.

The next example is from a post-cricoid carcinoma.

Fig. 3 is from a biopsy of the primary tumour. It shows a diffuse sheet of anaplastic squamous-cell carcinoma with many mitotic figures; the patient had a metastatic gland in the upper deep cervical group on the left side; it was about 1½ in. in diameter; a biopsy from it showed the same pattern.

Six months after radiotherapy the gland, although greatly reduced in size, was still palpable; it was removed. Fig. 4 shows its microscopic appearance. The tumour cells have degenerated and have become impregnated with calcium; the capsule of the gland can be seen separating it from the areolar tissues of the neck.

It is clear that X-rays or gamma rays exert a lethal effect at the cellular level. If the dose is sufficiently large, normal as well as abnormal tissues are adversely affected. The therapeutic effect is based on the lesser tolerance of many malignant tumours.

Turning to the clinical side, 30 consecutive patients suffering from extensive carcinoma of the larynx with fixed glands seen between January 1948 and February 1950 have been analysed. Of these, 6 are alive and judged to be free of disease on clinical grounds. All lead normal lives. 2 have a dense fibrosis of the sternomastoid on the side which contained a large fixed metastatic gland. They make light of their symptoms. The following is a short account of the history of 4 of these patients:

The first patient gave a history of sore throat and a lump in the neck of two months' duration. He had an undifferentiated carcinoma of the left aryepiglottic fold and a fixed gland about 2 in. in diameter low down in the neck on the left side, on the point of fungating through the skin. It is now three and a half years since treatment.

The second patient complained of hoarseness for six months and of a swelling in the right side of the neck for three months. He had an undifferentiated carcinoma of the right ventricle, ventricular band, spreading on to the laryngeal surface of the epiglottis. The right cord was fixed. There was a large fixed mass in the neck about 3 in. in diameter. He is free from recurrence four and a half years after treatment.

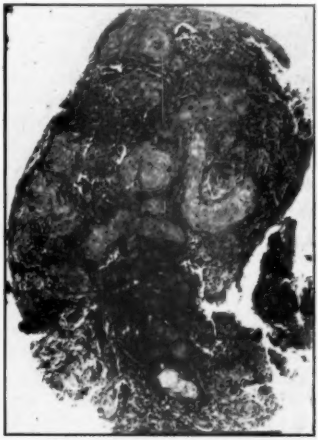


FIG. 1.—Biopsy of a squamous-cell carcinoma of œsophagus. × 50.

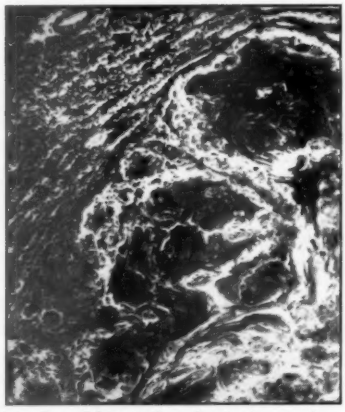


FIG. 2.—Metastatic gland six weeks after irradiation in the same patient as Fig. 1 (*see* text). × 50.

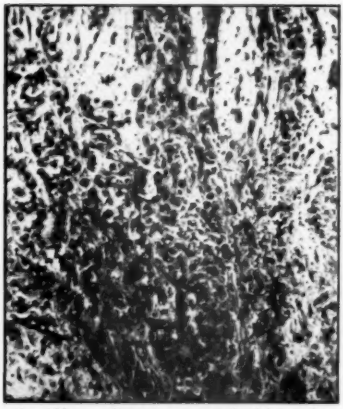


FIG. 3.—Biopsy from a post-cricoid carcinoma. × 100.

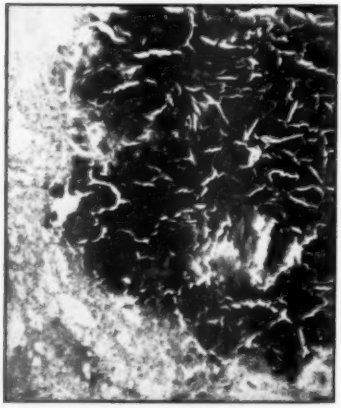


FIG. 4.—Metastatic gland in the same patient as Fig. 3 six months after irradiation (*see* text). × 50.

The third patient complained of hoarseness, dysphagia and a lump in the neck for four months. He had a growth filling the right pyriform fossa and the right cord was fixed; he also had a fixed gland in the right mid-cervical region of about 2 in. in diameter infiltrating the sternomastoid. He is alive and well three years after treatment.

The fourth patient gave a history of hoarseness for three years and of a lump in the neck for one month. The whole of the left vocal cord, ventricle and ventricular band and the lower part of the aryepiglottic fold were involved by an undifferentiated squamous-cell carcinoma. He had a fixed gland in the left mid-cervical region. He is now free from disease four years after treatment.

This survival rate, such as it is, is higher than might be expected. Measured against the absolute incidence of inoperable carcinoma of the larynx and pyriform fossæ with fixed glands, the five-year survival rate after treatment is very low indeed. Many of the patients in this group are debilitated, dehydrated, old and some are moribund. However when the patients are selected, mainly because they can withstand radical radiotherapy, some hope can be entertained for them. Fixed metastatic glands in the neck do not spell inevitable failure; their treatment, in selected cases, is a practical proposition which is effective in a small minority of patients.

I am indebted to Dr. K. T. Weavers for the interpretation of the slides and the preparation of the photomicrographs.

Mr. J. F. Simpson said he would like to illustrate some points from a case of carcinoma of the larynx in a man now aged 82. The tumour had spread across the mid-line and was partially subglottic. A biopsy showed it to be a well-differentiated squamous-cell carcinoma. Laryngectomy without block dissection was performed in May 1951.

Nine months later a gland in the neck presented. This subsequently proved to be anaplastic in type, illustrating the point that the primaries and secondaries may not tally in respect of the Broder classification, so rendering this grouping of little use as a factor in the planning of treatment.

In the course of the block dissection carried out to deal with this cervical metastasis the gland was found adherent to the carotid trunk in the region of bifurcation.

In 2 previous cases in which a similar condition was found the gland had been dissected off the vessels but in each case at a later date the artery gave way as the neoplasm had invaded the arterial wall. In this case it was decided to ligature the external carotid and to resect adjoining portions of the common and internal carotid so that a segment of about 3 cm. was removed with the gland.

An immediate end-to-end anastomosis was carried out by Mr. H. H. G. Eastcott and completed in about twenty minutes. The patient made a full recovery without any untoward result from having his common and internal carotid clamped.

Six months later the patient presented a mass rising into the neck from below the clavicle. This was treated by radiotherapy and, so far, appears to have been controlled. It is now two years since the patient had his laryngectomy.

This case helps to show that even fixation of the growth to the carotid trunk may not necessarily render it inoperable.

Mr. Ronald Macbeth said that laryngologists should be just as keenly interested in the treatment of cervical metastases as they were in that of the primary malignancies. The main lesson to be drawn from such cases was that however successfully the primary was treated there was always a fear that the metastases might defeat them. Consequently laryngologists should be ready to carry out whatever operations were needed and should retain the last word in the assessment of treatment. Mr. Lewis had rightly emphasized the place of radical neck dissection in extrinsic laryngeal lesions.

Operation and irradiation were not to be regarded solely as alternatives, but irradiation could be given after a radical neck dissection just as was the custom after radical breast surgery.

Contrary to standard teaching there was a case, on occasion, for doing a radical neck dissection for the metastases first, while these remained operable, and commencing irradiation of the primary lesion ten to fourteen days later. There might be some special reason for avoiding operation upon the primary, while to delay operating on the secondaries until the skin of the neck had recovered from irradiation might be fatal.

Mr. Munro Black said that there might be an objection to dissecting first and giving the radiotherapy afterwards. He thought the radiotherapists liked to have a lesion with an intact blood supply and would raise objections to applying irradiation after surgery, although it was true that many had their cases irradiated after operation and he thought that some people felt that this method improved results. The only thing he felt would be justifiable for neck gland metastases would be to apply the irradiation *first*. Resection could be carried out afterwards to extirpate any residual growth. He was interested to see that after several efforts a surgeon admitted himself to be defeated and the radiotherapist to be of some use.

He pointed out that surgical extirpation was not curing that lesion; it was accepting the fact that it was incurable in situ and that it must be removed. One could cure the patient, but one could not cure the lesion. He thought it might be worth while to attempt cure in situ first. No one had mentioned interstitial irradiation in these cases; it *could* cure, and if it failed, the surgeon could still extirpate the residuum.

Professor F. C. Ormerod considered that the division of cancer of the larynx into intrinsic and extrinsic types should be abolished. This classification had a long history but as it had no relation to the lymph-catchment areas or drainage system it was of little practical value.

The occurrence of lymph-node metastases from cordal tumours was not more than 4%, from subglottic tumours 12–15%, and supraglottic tumours 40%. In the absence of palpable metastases a block dissection of the neck was unnecessary in association with laryngectomy in cordal cases and in subglottic ones, but essential in supraglottic cases. It was advisable to do this at the same time as the laryngectomy and to remove the larynx and the cervical tissues in one mass, so that no lymph vessels that might be carrying cancer cells were cut across.

If the disease had spread across the mid-line it was advisable to clear all the lymph areas out of both sides of the neck, leaving the internal jugular vein, unless obviously invaded, on the heterolateral side.

If a carcinoma of the larynx was being treated by irradiation and there was an involved lymph node lying in the field of irradiation, the malignant cells in this node would, in many cases, be destroyed. If, however, a node became obviously involved after treatment by irradiation it was unlikely to be controlled by irradiation and should be treated by surgical methods.

Mr. R. D. Owen gave as his experience that a wide-field block dissection of nodes was rarely necessary where the growth was localized inside the laryngeal box. He always performed laryngectomy for carcinomatous lesions in the subglottic space, the anterior commissure with a subglottic spread, and a vocal cord lesion with fixation extending above and below the cord. Never did he perform a block dissection at the same time unless nodes were palpable in the neck at the time of operation.

There was one point he would like cleared up, and that was the question of what to do when it was decided to irradiate the primary lesion and where there were palpable and operable glands in the neck at the same time.

Mr. Durden Smith had mentioned that he was not in favour of a primary block dissection to be followed by irradiation of the primary lesion. Mr. Owen could not agree with this. He could recollect several occasions where a primary lesion with operable nodes had been irradiated and the local reaction following this had been such that valuable time had to be wasted before the condition of the patient—both local and general—was good enough to enable one to proceed with a block dissection, and even then only to find that the secondary mass had become inoperable.

His practice was that when nodes were operable he removed them, not by a partial block but by complete block dissection, and bilaterally if necessary. The neck could be healed and ready for irradiation of the primary within two or three weeks at the latest.

This teaching could apply to a pyriform fossa lesion with operable nodes. Although he always advised laryngectomy for a pyriform fossa carcinoma, there were occasions when the patient refused to part with his larynx and preferred to chance irradiation first; but what about the operable palpable nodes? Surely the best treatment was not to lose the opportunity to remove them while they were operable. There was really no need to worry about the blood supply to the skin flaps, or the opening up of lymphatic fields. This could be proved by experience.

He had 5 cases of pyriform fossa carcinoma that had block dissection followed by irradiation of the primary. The whole 5 came back within five years, with recurrence of the primary, but with no recurrence in the neck. 4 of these had partial pharyngo-laryngectomy done over five years ago, and 3 of them were still alive and well.

He felt that it was not wrong to deal with operable glands first and then to irradiate the primary afterwards.

Mr. Lewis, in reply, said that there seemed to be a general measure of agreement. It was an important principle that the common carotid could be sutured and the part which had been involved by a growth removed. This would save a number of cases. They were not all as fortunate as Mr. Simpson in having vascular experts working in the next theatre! It had been suggested that instead of joining the common carotid if there was a gap, the distal end of the external carotid could be joined to the distal end of the internal carotid and so get the flow of blood diverted to the internal carotid and thence to the brain, which might help to prevent cranial complications.

In reply to Mr. Macbeth he did not advocate block dissection for all intrinsic carcinomas of the larynx but only for extensive supraglottic cases. An intrinsic supraglottic cancer, if mobile and small, he thought could be treated by deep X-rays, the gland area being watched carefully and a block dissection done if suspicious thickening occurred.

Mr. Durden Smith, also in reply, said that Mr. Owen had outlined a case in which metastatic glands were present and in which X-ray therapy was regarded as the method of choice in the treatment of the primary lesion. The difficulty here was that it entailed too much delay before block dissection could be undertaken. The problem differed from that of buccal cancer in that there were in the latter quick methods of radiation treatment which enabled block dissection to be done within a fortnight of the primary treatment. There was a case here for block dissection before X-ray treatment to the primary. But the radiotherapists with whom he had to do inveighed very heavily against the irradiation of primary lesions through tissues whose blood supply was attenuated. Even with the normal blood supply the effect on the neck with high dosage was severe, and they disliked having to irradiate in those circumstances.

Section of Odontology

President—E. WILFRED FISH, C.B.E., M.D., F.D.S. R.C.S.

[*January* 26, 1953]

The Incidence, Nature, and Clinical Significance of Palatal Invaginations in the Maxillary Incisor Teeth

By Professor G. E. M. HALLETT, M.D.S., F.D.S. R.C.S., H.D.D.Ed., L.D.S.

IT is quite obvious, clinically, that caries in or about the palatal cingulum pit occurs with considerable frequency and the carious focus seems to be the pit itself (sometimes called the foramen cæcum) (Fig. 1).

Again, some of these teeth give depressed vitality reactions—though soon after eruption the point of a fine probe applied to the pit in the cingulum of the tooth may cause acute pain as if an exposure of the pulp were present. Occasionally it has been noticed that a patient presents with an apparently normal incisor—usually a second maxillary—which, without any history of trauma or carious cavitation, has become abscessed, or failed to complete root development, or both (Fig. 2). The matter becomes of great clinical importance if it can be shown that these developmental defects are present in a significant proportion of all cases, for the second maxillary incisor is a most important member of the dentition æsthetically and replacement by artificial means in the young person is a formidable problem.

During the course of this investigation a classification of invagination was adopted dependent largely upon degree of affection. It is realized that the Classes I–IV (in Group 1a) are an artificial arrangement and that many specimens may occur that fall between, but some assessment of degree was necessary for charting purposes, and all doubtful cases were referred to the next *lower* group.

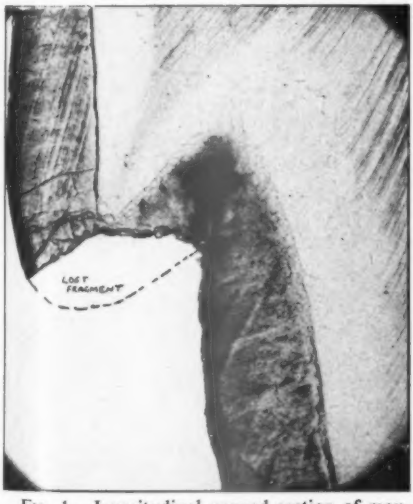
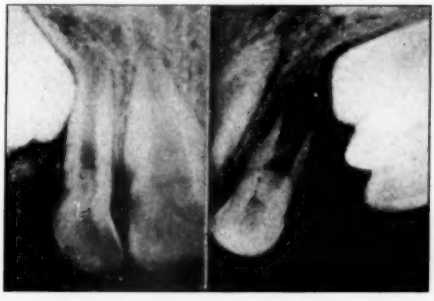


FIG. 1.—Longitudinal ground section of maxillary second incisor extracted for orthodontic reasons. A Class II invagination is present and early caries can be seen in the pit. A portion of the enamel has been lost during the preparation.



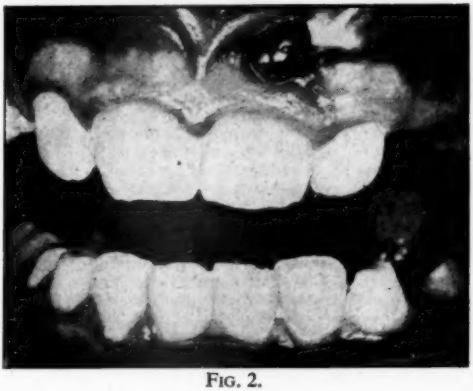


FIG. 2.—Class III invaginations in $\underline{2}|\underline{2}$. Death of pulp, abscess formation and incomplete root development in $|\underline{2}$. No history of trauma. $\underline{2}|$ has been filled and has since then completed apical closure.

Our preoccupation has been with Classes I–IV of coronal invaginations occurring from the palatal pit, these being the "regularly occurring phenomena", and the other forms of dens invaginatus, as we prefer to term the malformation (rejecting dens in dente, gestant, and other inaccurate if long-used descriptions), will be mentioned only in so far as it is necessary for the development of our argument.

General Classification

Dens invaginatus simplex (single enamel-lined sacculus).

1. Arising from foramen cæcum (normal labial crown-form)
   - (*a*) Coronally limited, Classes I, II, III, IV (Figs. 3 and 4).
   - (*b*) Invading radicular pulp-chamber.
2. Arising from incisal edge.
   - (*a*) Conical crown — (i) Coronally limited. (ii) invading root. (iii) dilated types.
   - (*b*) Tuberculated crown. — (i) Coronally limited. (ii) invading root.
3. Combined with supernumerary element.
   - (*a*) Partially fused.
   - (*b*) Wholly fused.

Dens invaginatus complex (multiple lined sacculi)

Very rare replacement or supernumerary types.

(Miller's specimen 1901.)
(Archer's specimen 1950.)

FIG. 3.—Skiagrams showing the four classes of invagination.

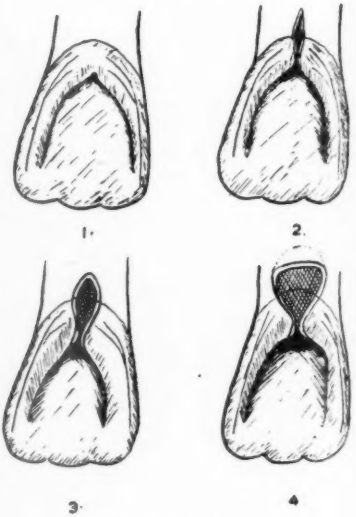


FIG. 4.—Diagrammatic representation of the four classes.

Classification of Invaginations

I. A definite cleft is formed in the palatal enamel at cervical level. This cleft runs vertically and there is no expansion or dilatation. The fissure stains darkly and the point of a sharp probe may stick in it. Caries is slow but develops steadily over a period of years. Fig. 4 (1).

II. The invagination extends towards the pulp chamber and a definite pit is formed in the cingulum. In the radiograph the invagination has a "tented" appearance. There is very slight or no dilatation and caries is not infrequent. Fig. 4 (2).

III. The invagination extends deeply into the pulp chamber and is dilated. Extension may be beyond the amelo-cervical junction. The pulp chamber extends around the invagination except on the palatal aspect. The enamel lining may be complete or may fail in the deepest portions of the cavity. These teeth usually develop caries, and may often suffer premature death of the pulp with incomplete root formation following infection from the mouth. Fig. 4 (3).

IV. The invagination apparently occludes the whole of the coronal pulp chamber and may extend beyond the amelo-cemental junction level. There may or may not be a heavy deposit in the form of a "cap" on the involuted portion. The dilatation is greater than in Class III cases and often has a characteristic "flat-top". The same clinical considerations apply as in Class III cases. Fig. 4 (4).

The literature on this subject is inextricably bound up with that of dilated, gestant, and other types of odontomes which are loosely referred to as dens in dente. It starts with "Socrates" writing in the *Dentists Register* (1856) and in 1859 Tomes described both the deeply invaginated types arising from the incisal edge and those arising from the palatal pit. Busch (1897) coined the term "dens in dente" believing two dental elements to be involved. In 1934 Kronfeld reported more extensively upon the phenomenon and suggested that the term "dens in dente" be dropped. His article marked the beginning of a new interest in invaginated teeth and since then there have been numerous, but usually short, communications on this subject, nearly all stimulated by the occurrence of a deeply invaginated or dilated type.

Bilateral occurrence has been noted as of great rarity and in 1947 Swanson and McCarthy reported what they believed to be the first case of this nature. Since then a few further bilateral cases have been reported (Searcy, 1948; Rabinowitch, 1949; Archer and Silverman, 1950; Townend, 1949). The following investigation will show that the type of invagination under review is predominantly bilateral. The only authors to call attention to the phenomenon as a clinical problem of greater frequency than generally realized, are Atkinson (1943, 1949), Rabinowitch (1949) and Townend (1949).

Taylor (1951) has reviewed a case of invagination from the palatal pit, and Munro (1952) published some similar cases from the records of the Dundee Dental Hospital.

Rushton (1936, 1937), Sprawson (1937), Colyer (1926), Bøhn (1948), Gustafson and Sundberg (1950), Kronfeld (1934) and others have described specimens usually of the "dilated" and "gestant" types, and have given various accounts of their histogenesis.

The investigation.—Quite early in the investigation it became apparent that there would be some difficulty in deciding exactly what is a normal incisor, so wide were the variations discovered. About half of all incisors conform to an ideal morphology, in that the medial and distal palatal ridges of the crown merge imperceptibly into one another in the cervical region and the cervical bulge so produced blends smoothly into the palatal concavity. There are no pronounced furrows or pits. In the other 50% there is a wide variety of palatal patterns produced by the different manner in which the medial and distal ridges are raised up and coalesce cervically. Clinically, a longitudinal fold may be produced, or there may be a pit of varying dimensions surrounded by enamel ridges of varying heights. These may be so high as to form accessory cusps and these cusps may be of two types. They may be *asymmetrical* being produced from the lateral ridges, or *median* by elevation of the cingulum enamel. The pits or folds may not catch the point of a fine probe and may never become a caries focus. In others the probe point sticks quite definitely, whilst some are frankly carious.

Two different sources of material were examined. One was of senior school children using ordinary visual and tactile methods. The other was of a series of skiagrams taken from the records of the Children's Department, Newcastle Dental Hospital.

The clinical examination.—Senior children were examined, as the minimum age would be 12+, the incisors would have had some time for pre-carious fissures to stain, and for caries to develop in others. There was the slight disadvantage that more incisors would be missing from caries and traumatic injuries, but it was felt that this would not be an unduly high proportion and that such teeth could be noted and considered as negative as regards this investigation. 400 children were examined, there being an almost equal number of boys and girls. Each of the upper incisors was examined carefully with mirror and probe, and charted separately under the following headings:

(1) Fold (longitudinal cleft with no localized pitting).
(2) Pit.
(3) Caries (this was only registered for both fold and pits if the probe stuck, or if there was unmistakable caries, or a filling already present).
(4) Cusp (accessory).
(5) Fractured.
(6) Dead teeth.
(7) Missing teeth.
(8) Diminutive and malformed.

These findings are given in Tables I and II.

TABLE I.—CLINICAL EXAMINATION 400 MIXED PUPILS W.B. GRAMMAR SCHOOL

	2|	1|	|1	|2
Fold	44	18	17	44
Pit	93	10	8	92
Caries	55	6	8	61
Cusp	5	—	1	5
Fracture	2	21	20	1
Dead	—	6	6	—
Missing..	7	6	3	3
Diminutive	5	—	—	6

TABLE II.—CHILDREN EXAMINED FOR PALATAL FAULTS, &C., AT W.B. GRAMMAR SCHOOL

No. of children examined age 12–17		400	197M	203F	
Possible number of incisors		1,600			
		400	400	400	400
		2| |2	1|	|1	|2
Folds	%	11·0	4·5	4·25	11·0
Pits	%	23·0	2·5	2·0	23·0
Caries and pre-caries	%	14·0	1·5	2·0	15·0
Filled or urgent	%	2·5	1·0	1·0	3·25
Diminutive	%	1·25			1·25
Combined fold-pit	Teeth	137·0	28·0	25·0	136·0
	%	34·25	7·0	6·25	34·0
No. of children positive showing a pit or fold in one or more incisors		158 out of 400 or 39·5%			
Teeth missing, caries, trauma, &c.		7	6	3	7
Total 23 or 1·41% of 1,600 possible No.					

The radiological examination.—Though many of the children are X-rayed at the Dental Hospital for orthodontic reasons, it was felt that this would not specifically alter the issue in this investigation unless one were to include incisal overcrowding as a factor in the ætiology (Euler, 1939; Atkinson, 1943). The number of children attending for congenital partial anodontia, supernumerary teeth and rarer pathologies, is of course higher than in ordinary practice, or to be found, say, in the Grammar School examined, but it was not felt that, for the special purpose in hand, the cross section would be significantly unrepresentative. In any case, this would be confirmed or otherwise by the Grammar School findings. It should be mentioned that all the age groups from 2–15, and the sexes, were randomly mixed in the radiological examination.

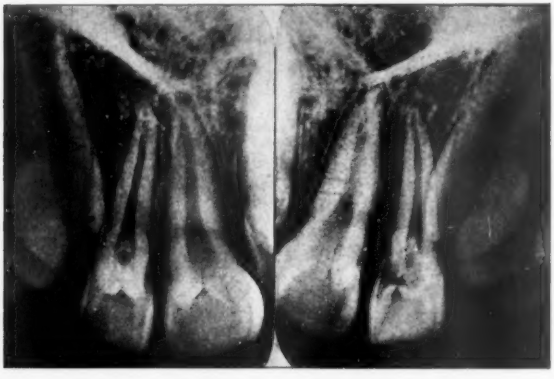


FIG. 5.—Class III invaginations present in 2|2 associated with Class I invaginations in 1|1. This case would have been recorded as 3—1—1—3 by the author's notation. An orthodontic problem is also present, 3|3 being blocked out of the arch.

It was necessary to examine a large number of skiagrams to obtain sufficient material, some having to be rejected on account of:

(*a*) Insufficient development of the incisal crown.
(*b*) Rotation of crowns.
(*c*) Missing teeth.
(*d*) Root filled teeth.
(*e*) Poor skiagrams due to movement on the part of the patient.

In all, 2,000 X-ray envelopes were examined, producing 586 cases where the quality of the films was adequate for a diagnosis to be made. If, for causes (*a*) to (*e*) previously cited, the data was inadequate the case was rejected and refiled. If there were clear skiagrams of the upper *four* maxillary incisors, it became one of the total of 586 and was pronounced negative or positive according to whether one or more incisors conformed to the writer's classification (*see* Figs. 3 and 4) or not. If positive, the individual incisors were classified I . . . IV (Fig. 5). If there was any doubt as to the classification, the next *lower* group was inserted.

It was found that, for the most part, the distribution of the invaginations amongst the incisor teeth was symmetrical, though in a few cases only one side showed the invagination, whilst the corresponding incisor of the other side was apparently normal.

The results were therefore tabulated in two groups:

(1) Symmetrical distributions; (2) Asymmetrical distributions (*see* Tables III, IV and V).

TABLE III

Total No. of cases examined 586 of which 295 were negative, 291 were positive — 49·616%

Total No. of teeth examined 2,344 of which 1,180 were negative, 758 were positive — 32·34%

Distribution of classes of invagination in each of the upper incisors

	2|	|2	Total	1|	|1	Total
Class I ..	151	151	302	73	72	145
Class II ..	97	97	194	16	16	32
Class III ..	27	25	52	3	2	5
Class IV ..	12	14	26	1	1	2
	287	287	574 Teeth	93	91	184 Total 758 teeth

TABLE IV.—DISTRIBUTION OF INVAGINATIONS IN ORDER OF FREQUENCY

1. SYMMETRICAL

2|	1|	|1	|2	Cases	Cases % of total	Teeth 2,344 total
1	0	0	1	112	19·1	224
2	0	0	2	60	10·24	120
1	1	1	1	37	6·3	148
2	1	1	2	23	3·92	92
3	0	0	3	13	2·22	26
2	2	2	2	9	1·536	36
3	1	1	3	7	1·19	28
4	0	0	4	4	0·68	8
3	2	2	3	3	0·51	12
4	2	2	4	3	0·51	12
4	1	1	4	2	0·34	8
3	3	3	3	1	0·17	4
4	3	3	4	1	0·17	4
4	4	4	4	1	0·17	4
0	1	1	0	1	0·17	2
1	2	2	1	1	0·17	4
				278	47·396% 47·4%	732
Add ASYMMETRICAL. *See* separate table				13	2·22	26
				291	49·616%	758
Total Class III and IV cases including asymmetrical				42	7·167	85 3·63% of 2,344 teeth
2nd incisors						78 6·66% of 1,172 teeth
1st incisors						7 0·6% of 1,172 teeth

TABLE V

2. ASYMMETRICAL

2|	1|	|1	|2	Cases	Teeth
0	0	0	1	1	1
0	0	0	2	2	2
1	0	0	2	1	2
2	0	0	0	2	2
3	0	0	0	1	1
3	1	1	1	1	4
3	3	0	3	1	3
2	0	0	4	1	2
2	1	0	4	1	3
4	0	0	2	1	2
2	1	1	4	1	4
				13	26
Add SYMMETRICAL cases				278	732
				291	758

There were 278 of the former as against 13 of the latter, thus demonstrating a very strong tendency towards symmetry (21 *to* 1). This must be an important factor when considering ætiology. Another interesting point which emerged was that in almost every case in the symmetrical distributions, the maxillary second incisor was also affected if the first incisor showed either folding or invagination, and in most cases was more severely affected. In only 2 cases were these conditions reversed, i.e. where the central incisors showed a deeper invagination than the second incisors.

DISCUSSIONS UPON THESE FINDINGS

It was beyond the scope of this investigation to correlate the different degrees of invagination with caries incidence. Were all the 586 cases examined at the Grammar School recalled each year for a period of ten years some informative data could no doubt be obtained, but, allowance would have to be made for teeth lost from other reasons such as trauma, extension of medial and distal caries, and

so on. Also, for this purpose it would be better to take a large group of 8-year-old children rather than the mixed age groups included in the above survey, as they could then be followed through the remainder of their school life.

Whether invaginated teeth with their inherent weakness become carious at the site of the palatal pit soon after eruption or late, will depend largely upon the individual caries susceptibility.

For example in the case illustrated in Fig. 6 a similar degree of affection was present in the four maxillary incisors and although this patient was at the time of the photograph only 12, well-established caries was already present in the first incisors which in a short while would have led to pulpal exposure and infection. Occasionally one sees cases of Classes III and IV invaginations where, by the age of 16, there has been no filling inserted or signs of pulpal death. Nevertheless, so many pulpal deaths have been observed by us where invaginations have been present and no other apparent responsible cause that it must be considered neglectful to leave them untreated. It is here that the investigation of the Grammar School helps.

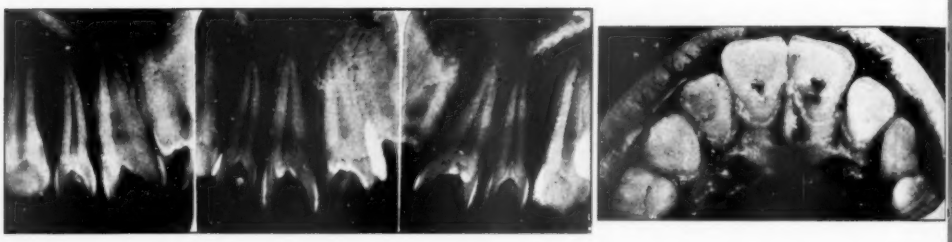


FIG. 6.—Class II invaginations in the four maxillary incisors of a boy of 12. Notation 2—2—2—2. The caries susceptibility is high and all the invaginations are carious, especially $\underline{1|1}$ which have been erupted longer than $\underline{2|2}$.

Out of 1,600 possible incisors 130 or slightly over 8%, showed active palatal caries (judged by deep staining or the sticking of the probe point). Of the 130 teeth affected 116 were second incisors and 14 were first incisors. If these figures are examined separately we have:

First incisors (14 out of 800) 1·75%. Second incisors (116 out of 800) 14·5%.

The special tendency to invagination of the second incisors is manifest, being over *eight* times that of the first incisors. If we now turn to the radiological survey and take Classes III and IV invaginations together we find that 85 out of 2,344 incisors or 3·61% were affected. Taking these figures separately for first and second incisors we have:

First incisors (7 out of 1,172 teeth) 0·6%. Second incisors (78 out of 1,172 teeth) 6·66%.

These percentages are almost exactly half those given above for cariously affected invaginations at the Grammar School, so that, assuming a similar distribution of the four degrees of invagination amongst the incisors of the pupils there (and this could only be established by X-ray examination) the conclusion must be drawn that palatal pit caries is spread over all the four degrees and that Classes III and IV types must not be considered as peculiarly susceptible. This observation does not, however, apply to their susceptibility to pulpal infection and death which can take place in the total absence of caries. Almost all the cases of which the writer has experience in which this has occurred have been in the more severe forms of invagination, and have occurred in young patients. By grouping Classes I and II invaginations together and comparing their incidence with Classes III and IV grouped together we have:

Classes I and II invaginations 249; Classes III and IV invaginations 42; out of 291 cases.

That is to say, Classes I and II invaginations taken collectively are nearly six times more frequent than Classes III and IV taken collectively. A further comparison between the figures obtained from the Grammar School survey and that carried out on the X-ray files of the Children's Department can be made.

Referring to Table II it will be seen that the number of children at the school who had either pits or folds in one or more teeth were 158 out of 400 or 39·5%.

The radiological survey showed that 49·6% had some degree of invagination in one or more incisors. This means either that:

(*a*) the X-ray files were weighted to the extent of 10%; or

(*b*) a further 10% of the cases could have been discovered had it been possible to X-ray all the incisors at the Grammar School.

We have repeatedly noticed that invaginations not readily detectable by visual and tactile methods of examination can be positively identified by X-ray examination. Reasons have previously been given why it was not considered that the files examined at the Dental Hospital should be unduly

weighted and it seems reasonable that the figure of an extra 10% should be due to the greater efficacy of the X-ray method.

It seems, therefore, that the greater the degree of invagination the higher the tooth mortality, for though caries is spread over all Classes I – IV, Classes III and IV are, in addition, more susceptible to pulpal death.

Ætiology

Full discussion of the ætiology (still not understood) is outside the scope of this communication. Most of the writings have been concerned with the so-called dens in dente, or the gestant, and dilated forms of odontomes. Occasionally when reporting cases of this nature, authors have touched upon the coronally invaginated incisor. Some authors have suggested that all invaginations are the same basic phenomenon, the different forms being due to varying degrees of affection only (Gnamm, 1922; Colyer, 1926).

The various theories can be summarized as follows:

(1) That two teeth or two separate dental elements are involved. This view was originally held by Baume (1874); Busch (1897), who coined the term dens in dente; Lejeune and Wustrow (1920) who felt that it was an atavistic phenomenon supporting the concrescence theory; Herbst and Apfelstaedt (1939), and more recently Gottlieb (1948), who viewed invagination as a developmental defect arising during the fusion of the frontal and maxillary processes.

(2) That infection from a deciduous tooth is responsible (Fischer, 1936).

(3) That the condition is due to "growth pressures" (Euler, 1939; Atkinson, 1949).

(4) That the invaginations are an expression of atavism (De Jonge Cohen, 1919; Lejeune and Wustrow, 1920; Erausquin *et al.*, 1932).

(5) That traumatic forces have caused the anomaly (Hoepfel, 1936).

(6) That they are quite simply hamartomas or hamartoblastomas (Tratman, 1951).

Apart from Gottlieb most, or indeed all other dental authorities of the present day agree that only one dental element or unit is involved. It is, however, quite possible for a supernumerary element to be associated with a tooth subject to invagination when it can be clearly seen that the two phenomena are quite separate. Gottlieb's theory also seems untenable in view of the figures arising from this investigation. If it were due to failure of union of the frontal and maxillary processes this would hardly affect not only the second incisors bilaterally but also the first incisors with relative frequency. This should also serve to reject the infection theory which has only one fact to commend it, namely, that, so far, no case of invagination of the deciduous teeth has been reported. Growth pressures may seem a more attractive cause in these days of malocclusion due apparently to disharmony between size of teeth and supporting bone. Undoubtedly supernumerary and replacement types are frequently associated with invaginations and the premaxilla is the area most subject to supernumerary teeth. Nevertheless is it not difficult to find cases of severe invagination where the teeth are well spaced. Ten West African students were examined whose jaws and teeth were typically well developed and Class II invaginations observed in three of them (by X-ray). In 1 case the palatal pits were definitely carious to the probe. 57 cases demonstrating supernumerary teeth were examined and invaginations were detected in 27 or rather less than half. It would seem that invagination as an expression of inadequate developmental surrounding bone can hardly be supported.

The results of the investigation also discount the trauma theory of causation. This is not to say that occasional invagination of the enamel into the dentine is impossible, indeed in Salter's "Warty tooth" (1874), and in some of Gustafson's cases this was probably the prime cause. But the histological picture is different, being more like a sudden syncline and anticline in geological formation, and quite different from the ampulla-like invagination which occurs so regularly.

It seems probable then that these phenomena may be an expression of some powerful, if imponderable, tendency of phylogenetic origin. We do not know whether invaginations are on the increase or otherwise, and can therefore make no conjecture as to which way the tendency is being exercised.

Similar formations occur in the animal kingdom. The incisors of the horse and the zebra have strong points of resemblance. More particularly many of the quadrumania show a palatal grooving of the upper incisor teeth which seems normal for certain genera.

It is not known whether ancestral man was freer of these invaginations or not, but investigations by Montague (1940) suggest that primitive races have less incisal variations than "civilized" man.

It has not been found possible to extract any figures supporting or denying the recurrence of the invaginations on Mendelian principles of inheritance. Patients are themselves, of course, quite unconscious of their existence and therefore unable to give a positive history in parents, uncles, and so on. It is, however, a field worthy of investigation. For those interested in the complex story of tooth evolution, these invaginated incisors may form a significant part of the anthropological dental puzzle.

The actual mechanism of development of these invaginations is also obscure and a matter of considerable contention. It will be noticed that we differentiate in the classification between those invaginations arising from the foramen cæcum or palatal pit and those arising from the incisal edge. The invaginations under discussion are from the palatal pit. Dens in dente, dilated and gestant types

on the other hand appear to arise from the incisal tip. There are two opposing views about the mode of origin of these anomalies. One is that a proliferation of the cells of the internal enamel epithelium takes place, and these cells then invade the dentine papilla. There comes a time when they are unable further to sustain their continued growth through self-strangulation, as it were, in the region of the operculum. Tissue tensions develop within the invagination and, according to the way in which these tensions are maintained or increased, so the different forms of dilated teeth result. Rushton, Swanson and McCarthy, Tratman, Hoepfel, and others support the proliferation theory, and Rushton formerly likened it to an adenomatous type of hyperplasia but has since withdrawn this suggestion. Others, Kitchin (1935, 1949), Kronfeld, and Gustafson and Sundberg, suggest that rather than a proliferation of the internal epithelium, a local arrest of development occurs, the surrounding more actively growing cells then engulfing the laggard tissue with a similar resulting invagination.

Ultimate solution of this problem must await the amassing of sufficient histological evidence taken from early developing tooth germs at about the age of 7 months *in utero* onwards. Fortunately the invagination develops and calcifies *pari passu* with the rest of the tooth crown, so that the two most severe degrees can be diagnosed by means of the X-ray from a very early age and long before the actual eruption of the tooth in question (Fig. 7).

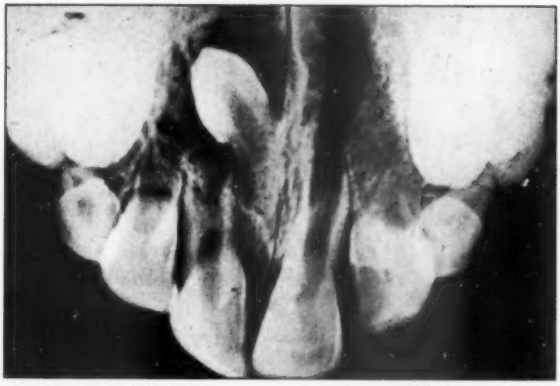


FIG. 7.—Developing Class III invaginations in unerupted 2|2. Mediodens also present.

It is our practice then in all malocclusion cases, incipient or established, and especially where extractions are contemplated, to scrutinize the maxillary incisors for presence and degree of palatal invagination as an important clinical factor to be weighed carefully in planning treatment.

BIBLIOGRAPHY

ADLER, P. (1939) *Dent. Items*, **61**, 418.
ARCHER, H., and SILVERMAN, L. (1950) *Oral Surg.*, **3**, 722.
ATKINSON, S. R. (1943) *Amer. J. Orthodont.*, **29**, 685.
—— (1949) *Amer. J. Orthodont.*, **35**, 830.
BAUME, R. (1874) *Mon. rev. dent. Surg.*, **2**, 396. Cited by Kronfeld.
—— (1877) Lehrbuch der Zahnheilkunde. Leipzig.
BØHN, A. (1948) *Acta odont. scand.*, **8**, 55.
BUSCH (1897) *Dtsch. Mschr. Zahnheilk.*, **15**, 469. Cited by Kitchen.
BOYLE, L. R. (1948) *Austral. dent. Congr.* (11*th*) *Proc.*, p. 336.
COLYER, F. (1926) *Proc. R. Soc. Med.*, **19** (Sect. Odont., p. 39).
DE JONGE COHEN, T. E. (1919) *Dent. Cosmos*, **61**, 224.
ERAUSQUIN, R., PELLIGRINI, A. J., and PONTE, J. J. R. (1932) *Rev. odont.*, **20**, 537. Cited by Kronfeld.
EULER, H. (1939) Die Anomalien, Fehlbildungen und Verstümmelungen der menschlichen Zähne. Munich.
FISCHER, C. H. (1936) *Dtsch. Zahn-, Mund- u. Kieferheilk.* Cited by Kitchin.
GNAMM (1922) Beitrag zur Kasuistik des "Dens in Dente". Inaugural Dissertation Tübingen. Cited by Bøhn.
GOTTLIEB, B. (1948) *J. dent. Res.*, **27**, 739.
GUSTAFSON, G., and SUNDBERG, S. (1950) *Brit. dent. J.*, **88**, 83, 111, 144.
HERBST, E., and APFELSTAEDT, M. (1939) Malformations of the Jaws and Teeth. London.
HOEPFEL, W. (1936) *Dtsch. Zahn-, Mund- u. Kieferheilk.*, **3**, 67. Cited by Adler.
HUNTER, H. A. (1951) *Oral Surg.*, **4**, 668.
KITCHIN, P. C. (1935) *J. dent. Res.*, **15**, 117.
—— (1949) *Oral Surg.*, **2**, 1181.
KRONFELD, R. (1934) *J. dent. Res.*, **14**, 49.
—— (1949) Histopathology of the Teeth. London; pp. 18–19.

LEJEUNE, F., and WUSTROW, P. (1920) *Dtsch. Mschr. Zahnheilk.*, **38**, 15. Cited by Kronfeld.
MILLER, W. D. (1901) *Dent. Cosmos*, **43**, 845.
MONTAGUE, M. F. A. (1940) *Hum. Biol.*, **12**, 323.
MUNRO, D. (1952) *Brit. dent. J.*, **92**, 92.
RABINOWITCH, B. Z. (1949) *Oral Surg.*, **2**, 1480.
RUSHTON, M. (1936) *Dent. Rec.*, **56**, 766.
—— (1937) *Brit. dent. J.*, **63**, 65.
SALTER, S. J. A. (1874) Dental Surgery and Pathology. London.
SEARCY, W. M., Jr. (1948) *Dent. Radiogr.*, **21**, 29.
"SOCRATES" (1856–1857) *Dent. Reg.*, **10**, 355. Cited by Kitchin.
SPRAWSON, E. (1937) *Brit. dent. J.*, **71**, 177.
SWANSON, W. F., and MCCARTHY, F. M., Jr. (1947) *J. dent. Res.*, **26**, 167.
TAYLOR, R. (1951) *N.Z. dent. J.*, **47**, 92.
TOMES, J. (1859) A System of Dental Surgery. London; pp. 227–228.
TOWNEND, B. R. (1949) *Brit. dent. J.*, **87**, 216.
TRATMAN, E. K. (1951) *Brit. dent. J.*, **91**, 167.

Acknowledgments.—My thanks are due to the photographic department of the Newcastle upon Tyne Dental Hospital for the clinical photographs. I am also indebted to Mr. A. E. Robinson, F.D.S. R.C.S., Senior Dental Officer, Northumberland Co. Council, for facilities for examining pupils at the Grammar School.

The Diagnosis, Clinical Significance and Treatment of Minor Palatal Invaginations in Maxillary Incisors

By RICHARD R. STEPHENS, B.D.S., M.R.C.S., L.R.C.P.

Department of Children's Dentistry, Institute of Dental Surgery, Eastman Dental Hospital

IF, as will be shown, the pulp of a maxillary incisor tooth with a palatal invagination is liable to suffer spontaneous death, it is valuable for the dental surgeon to be able to suspect from the appearance of the crown of an incisor tooth that such an invagination is present.

DIAGNOSIS

It would appear that only those teeth with the deepest cingulum pits are likely to be affected. Extracted upper lateral incisor teeth were taken at random and divided by crown morphology into three groups according to the depth of cingulum pit. The first group of teeth had no trace of cingulum pit whatsoever, the palatal surface being flat and smooth. The second group comprised those with the usual degree of palatal configuration and pit development, while in the third were placed those teeth only with very deep cingulum pits. Radiographs were then taken of these groups of teeth and it was found that the presence of invaginations was confined to those teeth in the deep pit group.

Therefore, although the presence of a very deep cingulum pit does not necessarily mean that an invagination is present, a tooth without such a pit is unlikely to be affected.

Unless caries has commenced in the deep pits of affected teeth, the point of a sharp probe will not necessarily stick in them although it may be trapped by the surrounding enamel walls.

The condition may be detected radiographically prior to the eruption of the tooth and in the majority of cases root formation continues to completion, eruption is unaffected and the response of the tooth to vitality tests in adult life is normal.

Invaginations appear to be more common in maxillary incisors in association with an abnormal crown form or with the presence of other developmental abnormalities of the dentition. Lateral incisors having a marked fossa on the mesial aspect and absence of the distal incisal angle frequently appear to be affected. In 2 patients invaginations in maxillary lateral incisors were associated with over-development of the cingulum cusps. Supernumerary teeth in the mid-line of the maxillæ were found in 5 out of 20 cases which showed palatal invaginations (as in Fig. 7 of Professor Hallett's paper). Another example of association with other developmental abnormalities of the dentition was a case showing bilateral invaginations in maxillary lateral incisors, with several premolars absent and the lower incisors represented by diminutive conical teeth.

There is thus an indication to take radiographs of upper lateral incisors in children when the crowns show very deep pits or some abnormal morphology and especially if, in addition, the dentition is affected by other developmental abnormalities such as supernumerary teeth or partial anodontia.

In relation to the diagnosis of this condition the following figures on incidence in patients at the Eastman Dental Hospital may be of value. Out of a series of routine full mouth radiographs on 150 patients with both upper lateral incisors present, 3 patients had bilateral invaginations in lateral incisors and 9 patients had unilateral invaginations. Thus 15 teeth were affected out of 300, an incidence of 5% of upper lateral incisors. Intra-oral radiographs taken of the upper lateral incisors in 1,000 patients were examined. Of these, invaginations were present in 36 teeth, and of these teeth, the radiographs of 9 showed definite periapical changes resulting from pulp death.

Clinical Evidence that Invaginations May Result in Spontaneous Death of the Pulp

The question arises as to whether pulp death does indeed result from an invagination or whether pulp death in these teeth may have resulted from some trauma to the tooth severe enough to cause apical vessel disruption and yet easily able to be forgotten by the patient.

The following 4 cases all lend support to the contention that spontaneous pulp death may indeed occur. None of these patients gave any history whatsoever of trauma to the teeth concerned.

Case I.—A girl aged 14 was one of a group of some 200 children being studied to assess various factors in growth and development. As part of the investigation routine lateral jaw radiographs were taken on each child. When the radiographs of this girl were studied, areas of rarefaction were detected over the apices of the maxillary lateral incisor teeth (Fig. 1).

Intra-oral radiographs showed bilateral invaginations in the lateral incisors with large periapical areas of rarefaction and the typical appearance of cessation of root formation (Fig. 2).

On clinical examination there were no signs whatsoever of periapical involvement. The patient had never had any symptoms from these teeth and was unaware that anything was amiss.

It can only be concluded in this case that spontaneous death of the pulps of both teeth occurred soon after they erupted and that symptomless chronic apical abscesses slowly developed.

More commonly, however, the patient presents because of symptoms of an acute exacerbation of such a chronic apical abscess or because, without other symptoms, a sinus has developed.

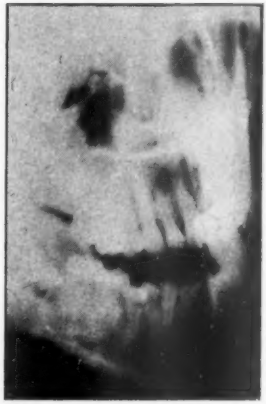


FIG. 1 (*Case I*).—Lateral jaw radiographs showing areas of rarefaction over both maxillary lateral incisors. (Radiograph kindly lent by Mr. G. J. Parfitt.)

FIG. 2 (*Case I*).—Intra-oral radiograph showing the periapical condition of the invaginated right lateral incisor.

Case II.—A boy aged 15 presented with the symptoms of a subacute apical abscess on the upper right lateral incisor.

The radiograph showed a long-standing apical abscess (Fig. 3) and an apicectomy was performed. Six months later the patient again complained of acute symptoms, this time on the left lateral incisor. The radiograph (Fig. 4) showed such a similar appearance to the previous one of the right side that they were then more carefully studied. It was noticed that both teeth had invaginations and that an occlusal radiograph taken at the first attendance but not carefully studied, did in fact show symmetrical chronic apical abscesses (Fig. 5).

Again it can only be assumed that spontaneous pulp death of both teeth occurred soon after eruption.

The process of pulp necrosis, including the development of the periapical lesion, was in the case of each tooth entirely symptomless, the patient presenting only when each chronic apical abscess in turn became the subject of an acute exacerbation.

It was this case that stimulated this investigation into the possibility of minor invaginations being the cause of pulp death.

Case III.—A girl aged 16 presented with a sinus over the upper right central incisor. The palatal aspects of all upper incisors showed deep pits. Neither the upper right central nor left lateral incisor responded to vitality tests, whereas all the other incisors did.

Radiographs showed invaginations in these two teeth only, and a chronic apical abscess had developed in the right central incisor (Fig. 6).

If, therefore, a tooth other than a maxillary lateral incisor has an invagination its pulp may die. Pulp death does not result from any peculiar characteristic of the lateral incisor alone.

Case IV.—This is another case illustrating the same point. The patient, an adult male, had typical invaginations in his upper lateral incisors. However, in addition all eight premolars had invaginations extending from their occlusal surfaces. Of these premolars, the pulps of the lower left first and right second premolars had died apparently a spontaneous death with subsequent chronic apical abscess formation. There was no

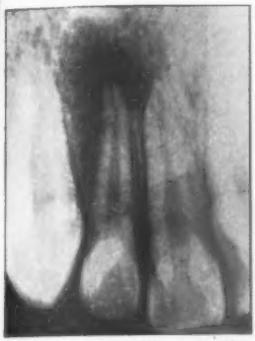


FIG. 3 (*Case II*). — Radiographic appearance of the right lateral incisor in a patient presenting with the symptoms of an acute apical abscess.

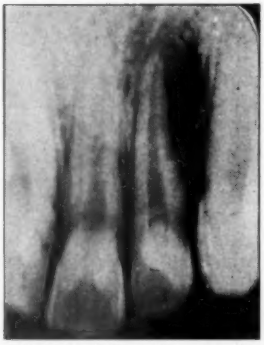


FIG. 4 (*Case II*). — Radiographic appearance of the left lateral incisor similar to that of Fig. 3. This was taken when the patient presented six months later, again with symptoms of an acute apical abscess.

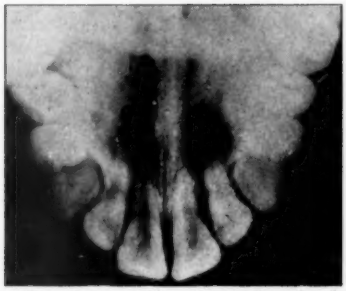


FIG. 5 (*Case II*). — Original occlusal radiograph showing bilateral areas of rarefaction of the same extent in association with both lateral incisors.

other explanation for the death of these pulps in this case. Fig. 7 shows an affected lower left first premolar. (The radiographs of this case were kindly lent by Mr. W. B. Balderston of University College Hospital Dental School.)

SEQUELÆ OF PULP IN INVAGINATED TEETH

It is usual for pulp death to occur before the root is fully formed and it is interesting to note that in the case of the upper lateral incisor the degree of root formation frequently corresponds with the normal stage of development of the root of this tooth as the crown erupts into the mouth.

Case V.—This illustrates well the usual time of cessation of root formation.

A girl aged 10 presented with an acute apical abscess associated with the upper right lateral incisor. There had been no history of trauma. The upper left lateral incisor reacted normally to vitality tests. Fig. 8 shows radiographs of both sides taken on the same occasion. Both teeth have invaginations. Root formation on the right side had ceased some time previously while on the left it has continued normally.

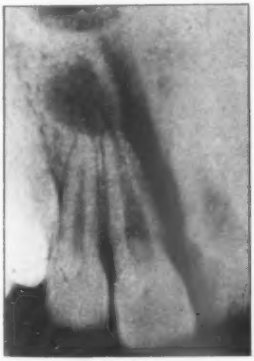


FIG. 6.

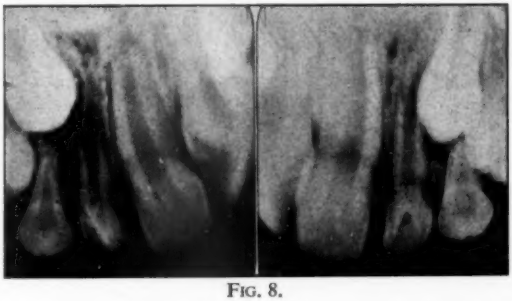


FIG. 8.

FIG. 7.

FIG. 6 (*Case III*).—The central rather than the lateral incisor has an invagination and a chronic apical abscess has developed.

FIG. 7 (*Case IV*). — Chronic apical abscess formation associated with a lower first premolar in patient with invaginations in all premolars in addition to maxillary lateral incisors.

FIG. 8 (*Case V*).—These intra-oral radiographs were taken on the same occasion. Root formation of the right lateral incisor has ceased following pulp death. That of the left lateral incisor has continued normally.

Pulp death and periapical lesions resulting from invaginations may often be quite insidious. The patient may not be aware that anything is amiss for many years until, for example, the symptoms of a dental cyst occur.

Routine radiographic examination of a girl of 13 revealed symptomless development of a small dental cyst over the period of three years four months as shown in Fig. 9.

Case VII.—An even more striking example of the insidious development of a periapical lesion resulting from an invagination is illustrated in Fig. 10.

The patient was a woman of 27 who presented with all the typical symptoms and signs of a large infected dental cyst associated with the upper left lateral incisor. The tooth can be seen to have a well-marked invagination and from the degree of root formation and size of pulp chamber and root canal it appears that the original pulp death occurred at about the age of 8 or 9.

A differential diagnosis must, therefore, be made between such radicular dental cysts and other cysts arising in this region such as the fissural and globulo-maxillary cysts.

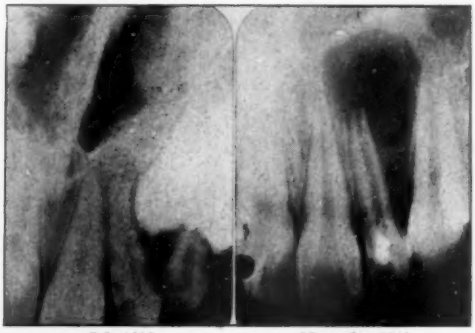


FIG. 9.

FIG. 10.

FIG. 11.

FIG. 9 (*Case VI*).—Development of a small dental cyst over a period of three years four months in association with a lateral incisor with an invagination. Root formation of the tooth is incomplete.

FIG. 10 (*Case VII*).—Large dental cyst in patient aged 27, resulting from pulp necrosis in an invaginated malformed tooth.

FIG. 11.—Longitudinal section of a maxillary lateral incisor showing the manner of cavity preparation and restoration to occlude the orifice of the invagination at the cingulum pit.

TREATMENT AND CLINICAL SIGNIFICANCE

An obvious prophylactic treatment to lessen the chances of pulpal necrosis is to close the orifice to the invagination as soon as it has passed the gingival margin during the course of eruption of the tooth. This may most easily be effected by preparing an undercut cavity in the cingulum pit to the thickness of palatal enamel only (Fig. 11). This may be filled with amalgam pressed on to soft oxyphosphate cement. Passage of the bur into the cavity of the invagination is to be avoided as the risk of pulp exposure is very great.

After restoration in this way the affected tooth should have periodical vitality checks and radiographic examination to observe continued root formation.

It is particularly important not to extract upper first premolar teeth for orthodontic reasons when the lateral incisors have invaginations until the condition of the pulps of the affected teeth has been assessed.

Another point of clinical significance is that if a patient presents for treatment of a chronic apical abscess or dental cyst associated with an upper lateral incisor and that tooth is seen to have an invagination, a radiograph should be taken of the other lateral incisor to exclude the possibility of a similar periapical condition.

SUMMARY

(1) The presence of invaginations in maxillary lateral incisor teeth may be suspected from the appearance of the palatal surface and possibly from the associations with other developmental abnormalities.

(2) There is clinical evidence to show that death of the pulp may be associated with non-carious invaginations.

(3) Pulp death may be followed by insidious development of a chronic apical abscess or dental cyst.

(4) Prophylactic treatment by occlusion of the invagination orifice at the cingulum pit is advised. The significance in relation to orthodontic treatment is noted.

Conclusions

It appears that spontaneous pulp death may occur in teeth with minor invaginations. This is often unnoticed by the patient. A chronic apical abscess or dental cyst may result and be discovered only on routine radiographic examination or because the patient presents with one of the various symptoms of such a periapical condition.

(38 clinical photographs and radiographs illustrated the original communication.)

The Pathology of Pulp Death in Non-Carious Maxillary Incisors with Minor Palatal Invaginations

By Ivor R. H. Kramer, L.D.S. R.C.S.

Department of Dental Pathology, Institute of Dental Surgery, Eastman Dental Hospital

A large number of papers have been published describing histological studies on invaginated teeth, but the majority of these have been on the grosser forms of invagination usually referred to as dens in dente. Gustafson and Sundberg (1950) review 68 previous communications. As Hallett has shown in Table III the smaller and less readily recognized invaginations (Hallett's Classes II to IV) are quite common, and it is this type of abnormality that forms the subject of the present study. The investigation was started when it was pointed out (Stephens R. R., 1951, personal communication) that the majority of permanent upper lateral incisors that had suffered "spontaneous" pulp death (i.e. pulp death in the absence of caries or a history of trauma) showed the radiological appearances typical of minor degrees of invagination. The purpose of the investigation was to determine the relationship between these two associated observations.

Method

Although many previous workers chose the ground section technique for the preparation of their material, it was considered that paraffin sections of decalcified specimens had overwhelming advantages, for by this method soft tissues are preserved and serial sections can be obtained. The only definite advantage of the ground section technique is the preservation of the enamel, but it was felt that, even in decalcified material, it might be possible to determine the distribution of the enamel within the invagination as enamel matrix is often preserved during decalcification in such protected sites.

Following radiographic examination to determine the anatomical features of the abnormality, each specimen was decalcified and serial paraffin sections prepared. The specimens of upper lateral incisors with palatal invaginations were cut in the labio-palatal plane; that is, in the long axis of the tooth at right angles to the labial surface.

Results

It was difficult to obtain a specimen of this type of abnormality prior to pulp death. However, in one instance such a specimen was obtained, extraction of the tooth being indicated because of gross root resorption in association with an unerupted canine. Fig. 1 shows a section of this specimen prepared as described. There is a palatal invagination of moderate size and a small cornu of the pulp extends for a short distance behind the invagination towards the palatal surface of the crown. The pulp shows no histological evidence of inflammation, the only abnormality being the presence of some calcified deposits near the base of the invagination. Such deposits were not found in other specimens.

The majority of specimens on section showed only necrotic tissue within the pulp space. However, it was noticed that there was evidence that abscess formation had preceded death of the pulp (Fig. 2). This observation was confirmed by the examination of further sections impregnated by the Gomori method for the demonstration of reticulin (Fig. 3). In such preparations the reticulin "scaffolding" of the pulp was clearly seen and close examination showed the typical appearance of an abscess wall in the region of the invagination. Although it has, so far, proved impossible to obtain a specimen with such a minor invagination in which an abscess has developed but death of the pulp has not supervened, further confirmation of the observation that abscess formation preceded pulp death was found following the examination of specimens showing more marked invaginations. Fig. 4 shows the pulp opposite an invagination extending towards the apex, and in this region an abscess has

FIG. 1.—Labiopalatal section through a permanent upper lateral incisor showing the palatal invagination and short pulp cornu passing palatally to the invagination. × 7·5.

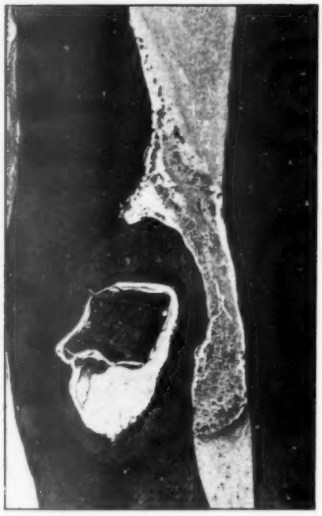


FIG. 2.—Although the pulp is necrotic there is evidence of abscess formation opposite the invagination. × 13.

developed. A further specimen, kindly provided by Dr. R. B. Lucas of the Royal Dental Hospital, showed an invagination with a bicornuate end, and an abscess had developed opposite each of the two cornua.

It is clear, therefore, that the development of an abscess in association with the invagination, whether minor or marked, was the cause of pulp death in many of these cases. The evidence also suggests that death of the whole pulp occurs very soon after the abscess forms, for there was no secondary dentine formation on either side of the abscess site. Furthermore, these abscesses were not sterile, for in every case large numbers of micro-organisms could be demonstrated. Although it is possible that the inflammation was originally non-bacterial in origin, the infection having resulted from localization of blood-borne organisms at the site of damage, it seems much more likely that bacteria had reached the pulp directly from the mouth.

An examination of the previous literature showed that, of the histological features observed in invaginated teeth, three might explain the penetration of micro-organisms from the mouth. Each of these theories was examined in relation to the minor degrees of invagination considered here.

(1) *Communication between the palatal pulp cornu and the interior of the invagination.*—If the region of the palatal cornu is closely examined in the original specimen with a vital pulp, it will be seen that there is a clearly demonstrable line of fusion in the dentine extending beyond the end of the pulp cornu (Fig. 5). This fusion with consequent limitation of the palatal cornu was commonly found, but in a few specimens such fusion had not taken place and a long slender extension of the pulp passed round the palatal side of the invagination. This extension often passed within 30–40 microns of the inner dentine surface of the invagination, but in no instance was any direct communication found despite the examination of serial sections. Therefore, it appeared that a direct communication between pulp cornu and invagination could not explain the development of the pulp abscess in the majority of cases.

(2) *Defects in the dentine between the base of the invagination and the pulp.*—It has also been suggested that there is commonly a defect in the dentine between the deepest part of the invagination and the pulp, and Rushton (1937) has shown, in a specimen with gross invagination, that such clefts in the dentine may be filled with enamel. In the minor degrees of invagination studied in the present investigation such a cleft or tubular defect in the dentine was found in only one case. The defect extended from the base of the invagination for a considerable distance into the dentine but did not actually reach the pulp (Fig. 6). In this instance, the space was not filled with enamel but with a collagenous material. Although a defect of this nature might well provide an easy pathway for organisms and thus favour the development of a pulp abscess, its presence in only one of 15 specimens showed that it was not the usual cause of pulp death.

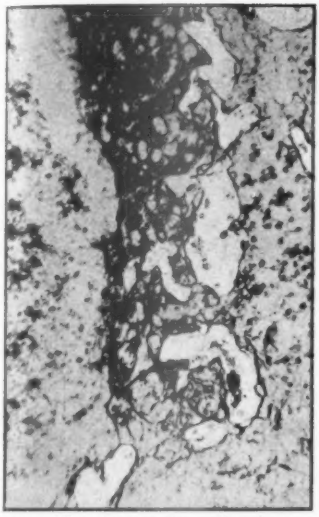


FIG. 3.—The abscess formation is seen more clearly when the reticulin scaffolding of the pulp is demonstrated. On the right can be seen the reticulin of the vessel walls, whilst on the left there is only the debris of the abscess cavity. Gomori impregnation. × 200.

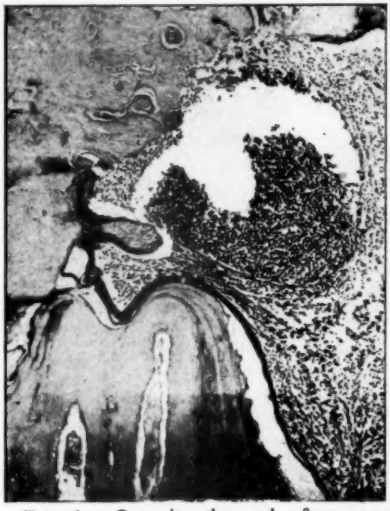


FIG. 4.—Opposite the end of a gross invagination passing upwards within the pulp space towards the apex there is a well-defined abscess. × 58.

FIG. 5.—A higher magnification of part of Fig. 1 shows the "line of fusion" in the dentine beyond the tip of the palatal pulp cornu. × 30.

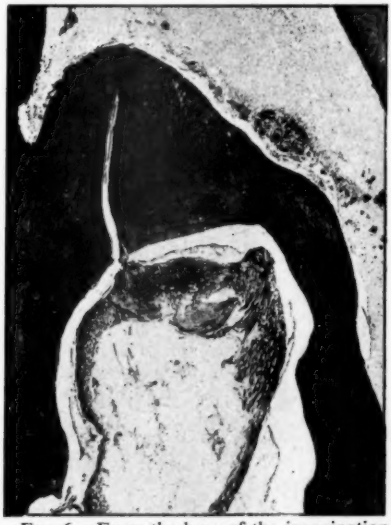


FIG. 6.—From the base of the invagination a defect in the dentine extends towards, but does not reach the pulp. This defect is quite separate from the palatal cornu and associated "line of fusion". × 30.

(3) *Defects in the enamel lining the invagination.*—Previous workers have described a defect in the enamel lining the invagination, a defect which may result in complete absence of enamel over a minute area of the dentine in the deepest part. This observation was repeatedly confirmed in the present investigation. In almost every instance it was possible to trace the position that the enamel

had occupied, and it was constantly noted that, in the deepest part of the invagination, the membrane covering the enamel elsewhere extended directly on to the surface of the dentine (Figs. 7 and 8). In one specimen showing a more marked invagination, clearly recognizable residues of the enamel organ ran down the centre of the invagination and degenerating ameloblasts could be seen closely applied to the dentine surface in one area (Fig. 9).

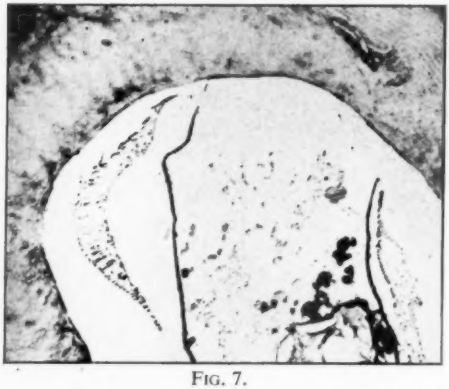


FIG. 7.

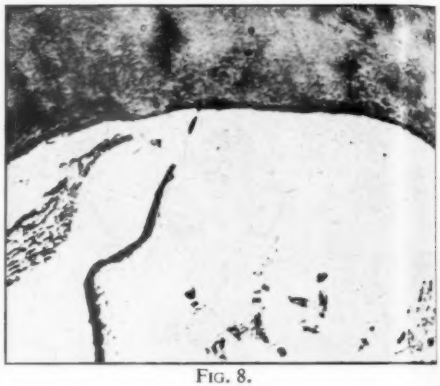


FIG. 8.

FIG. 9.

FIG. 7.—Running up the centre of the invagination is the space not occupied by enamel. This is bounded laterally by a membrane, beyond which can be seen residues of the organic enamel matrix. At the base of the invagination this membrane is applied directly to the dentine surface. × 144.

FIG. 8.—Higher magnification of part of Fig. 7. × 284.

FIG. 9.—Degenerating enamel epithelium applied directly to the dentine surface at the base of a gross invagination. × 203.

SUMMARY

(1) In permanent maxillary lateral incisors showing minor palatal invaginations, pulp death often occurs in the absence of clinical or histolog cal evidence of caries. (2) It has been shown that death of the pulp is preceded by the formation of a pulp abscess in the region of the invagination. (3) Although the palatal cornu of the pulp passing behind the invagination may come close to the dentine surface, no direct communication between this cornu and the interior of the invagination was demonstrated. (4) In only one specimen was it possible to demonstrate a pathway through the dentine from the base of the invagination towards the pulp. (5) It was constantly found that a minute area of the dentine at the base of the invagination was not protected by enamel.

CONCLUSIONS

It is suggested that, following eruption of the tooth and infection of the interior of the invagination, micro-organisms gain access to the dentine in an area unprotected by enamel. Following such bacterial infection, a pulp abscess develops opposite the area of infected dentine and ultimately leads to death of the pulp.

(The original communication was illustrated by 19 photomicrographs showing in detail each of the histological features described.)

REFERENCES

GUSTAFSON, G., and SUNDBERG, S. (1950) *Brit. dent. J.*, **88**, 83, 111, 144.
RUSHTON, M. A. (1937) *Brit. dent. J.*, **63**, 65.

Section of Radiology

President—CONSTANCE A. P. WOOD, M.A., M.R.C.P., F.F.R.

[*October* 17, 1952]

DISCUSSION ON SCLERODERMA

Dr. Edward R. Cullinan:

Scleroderma (Diffuse Systemic Sclerosis)

INTRODUCTION

Scleroderma, or hardening of the skin, is a wide term which may be applied to more than one clinical condition. Included in the term is the particular syndrome which is about to be discussed. This syndrome is characterized by sclerosis of the dermis of the hands spreading to the forearms, upper trunk and face, and, to a lesser extent, sometimes in the feet and legs. It is followed by or associated with changes throughout the gastro-intestinal tract and probably many other parts of the body. The dermal lesions, especially those in the extremities, may be accompanied by Raynaud's phenomenon, which, however, often precedes them for many years, phalangeal absorption, pigmentation, telangiectases and calcinosis. The syndrome is confined almost exclusively to women.

During the last three years I have had the opportunity of studying 14 patients suffering from this syndrome. I have been impressed in these and in other cases described in the literature by the striking constancy and similarity of the clinical features and of the course of the disorder. It is with these clinical aspects that I shall briefly deal. The radiological appearances will be described in detail by Dr. R. A. Kemp Harper.

NOMENCLATURE AND HISTORY

The syndrome is uncommon. It is generally assumed to be one of the collagen disorders, but its ætiology is unknown. Even the morbid pathology is ill-defined. Only slowly and recently has it been realized how widespread the lesions may be throughout the body. Probably, because of these facts, although the constancy of the manifestations and progress of the syndrome suggest that it is a disease *sui generis*, the naming of it has been confused and inadequate.

The gradual evolution of our knowledge of the disorder dates from Raynaud (1862) who was familiar with hardening of the skin accompanying the phenomenon he described in the extremities. Hutchinson (1896) drew attention to hardening of the extremities: acrosclerosis. One year later, Weber (1897) described the subcutaneous deposition of calcium salts in scleroderma, an observation which was lost sight of for thirteen years until Thibierge and Weissenbach (1910) rediscovered this calcinosis, describing 1 case of their own and 8 others from the literature. Basch (1932), a pupil of Thibierge's, redescribed the condition, and named it the Thibierge-Weissenbach syndrome. Garcin and others (1931) and Weissenbach and others (1935) claimed that it occurred exclusively in females and that the lesions were associated with the Raynaud phenomenon and the development of telangiectases. Meanwhile, Ehrman (1903) had remarked on œsophageal changes in scleroderma, a finding which was overlooked for twenty-eight years. Sellei (1931, 1932) and O'Leary (1943) recognized two types of dermatosclerosis: acrosclerosis and generalized. O'Leary and Waisman (1943) defined the differences between these two types, remarking that acrosclerosis affected women, that visceral lesions were common and the prognosis good, while generalized dermatosclerosis affected either sex, visceral lesions being rare and the prognosis bad. One year before this, Goetz and Rous (1942) had described a case of scleroderma with Raynaud's phenomenon, calcinosis, œsophageal spasm and duodenal ileus. Three years later, Goetz (1945), who had now seen 13 other cases, wrote an outstanding clinical record, elaborating the description of the syndrome and showing that lesions might extend down the gastro-intestinal tract as far as the colon, and that many other organs might be affected. He called it "Diffuse Systemic Sclerosis". More recently the skin lesions and œsophageal changes in 4 cases have been studied carefully by Bourne (1947, 1948, 1949) under the heading "Œsophageal Lesions in Sclerodactyly" and good clinical descriptions have been given by Ramsey (1951) of 3 cases, Littler and Canter (1951) of 1 case, and Truelove and Whyte (1951) of 4 cases, 3 of which had œsophageal lesions, under the title "Acrosclerosis". All their patients were women. A recent paper by Prowse (1951) entitled "Generalized Scleroderma with Intestinal Involvement" is of great interest because not only was death the result of paralytic ileus but the patient was a man.

Of the various terms and phrases used to nominate the condition, Diffuse Systemic Sclerosis seems the most useful title, at least until more is known of the essential nature of the disease. This is the term I propose to use.

The Material

My interest in diffuse systemic sclerosis was rekindled less than three years ago when I saw 2 patients suffering from the disease who complained of diarrhœa. On investigation both showed the sigmoidoscopic changes and radiographic appearances of the colon, which later Dr. Kemp Harper and I realized were typical of the disorder. These were exciting findings because, although œsophageal changes were well known, alterations in the lower bowel had barely been described. One of these 2 cases was introduced to me by Mr. E. S. Lee of the Westminster Hospital, to whom I am grateful. Dating from then I have now observed 14 cases, 6 under my own care and 8 under the care of my colleagues at St. Bartholomew's Hospital, whom I thank for allowing me to see them.

I have already remarked on the similarity of the clinical features and natural histories of these cases, not only to each other but to those described in the literature. This similarity is important, because it confirms the belief that diffuse sytemic sclerosis is a distinct disease entity. I shall confine my comments largely to the course of the disease, mentioning briefly the clinical findings. I shall neither speculate on the ætiology, nor discuss the pathological features, nor detail the many treatments tried: It is hoped to do this in a future communication.

Clinical Features

Age and sex.—All the 14 patients were women: 10 married and 4 single. Their ages when I first saw them ranged from 33 to 71, 8 of them being under 50.

Raynaud's phenomenon.—Raynaud's phenomenon was the first definite symptom observed by 10 of the 14 patients before the onset of acrosclerosis, although 4 of them spoke of having had cold hands or chilblains before this since childhood. All 10 had had the Raynaud's phenomenon in the hands and 6 of them had had it in the feet also, always less marked than in the hands, and often starting at a later date. The ages of 7 of these 10 patients when Raynaud's phenomenon was first noticed was from 23 to 30.

Acrosclerosis.—Acrosclerosis of the hands was invariable and the first real evidence of the disease. It became apparent to the patients at ages ranging from 24 to 61 and under the age of 50 in 10 of them. In general, it may be said that when acrosclerosis starts it always involves the hands. The feet are not always affected. When they are, the changes usually begin later and are never so severe as those in the hands. Then, gradually, the process creeps up the forearms, and perhaps the legs, and finally the face and upper trunk are implicated. All 14 patients first noticed acrosclerosis in their hands, and only 2 complained of it in the face at the onset. 5 of them remarked on it coming early to their feet, but always beginning later than in the hands. When I first saw the patients, one to twenty years from the onset of acrosclerosis, the hands and forearms were affected in all 14, the feet and legs to a lesser degree in 8, and the face and/or upper trunk in 9.

The clinical features of acrosclerosis are well known. All the patients showed the familiar findings. In the hands there are the thickening of the skin of the fingers, which is bound down to the underlying structures and cannot be pleated, the colour changes, and the tapering ends of the fingers which Sequeira said made an affected digit look like an elongated radish. Movement of the fingers is gravely limited and they become flexed at the metacarpophalangeal joints and tend to curl (Fig. 1).

As the lesion crawls up the forearms, the skin feels stuck over the ulnar bone.

Similar changes, though to a lesser extent, are seen in the feet and legs when these become involved.

Later, when the face is affected, the skin loses its natural creases and the mouth becomes more and more pinched up, ever decreasing in size. Partly because of this and partly because of the limitation of the movements of the jaw, the tongue sometimes can scarce be protruded. Mastication becomes difficult and is made even more so by the tightness of the skin of the neck which develops.

All these features are fully described in the literature.

Not infrequently, in all areas affected by acrosclerosis, but particularly on the face and upper trunk, there may be telangiectases and a patchy reticulated pigmentation.

Calcareous depositions in the involved parts are common, more so than is usually recognized, as we shall learn from Dr. Kemp Harper's communication. Clinically, one sees evidence of this in a chalky substance extruding from the fingers (in one patient this was the first symptom) and on points of pressure or of trauma. The extensor surface of the elbow is not an uncommon site (Fig. 3), and in one case there were extensive deposits in the buttocks.

During the course of the disease, ulcers were present on the hands of 9 of the 14 patients, but only on the feet and legs of one. Sometimes these were pin-point ulcers on the extensor surfaces of the fingers. Sometimes these were described as whitlows which would not quickly heal. At other times the ulcers occurred on the terminal part of the phalanges (Fig. 2) leading to necrosis and gangrene. The characteristic feature of most of these ulcers is to keep opening and healing.

In the areas affected by acrosclerosis, pain and stiffness round the joints, with marked limitation of movement, is a common finding. Truelove and Whyte (1951) pointed out that this may lead occasionally to confusion of diagnosis with rheumatoid arthritis; but, in fact, beyond the limitation of movement, there is no objective evidence of rheumatoid arthritis nor any real association with that disease.

Gastro-Intestinal Involvement

It was not altogether a surprise when Dr. Kemp Harper demonstrated radiological abnormalities of the œsophagus in all 14 cases, but it was startling to find radiological changes, often gross, in the colons of 8 out of the 11 patients examined.

Symptoms of gastro-intestinal involvement, which appears to be extensive in this disease, are less frequent than might be expected. 10 of the 14 patients complained of dyspeptic symptoms such as loss of appetite, flatulence, fullness after eating, heartburn and occasional vomiting. 7 of them only complained of difficulty in swallowing, worse with solids than with liquids. They said that food seemed to stick at the bottom of their gullets and was sometimes returned unchanged.

I have already remarked that the first 2 patients of this series had diarrhœa, but they were the only 2. Constipation was the more usual complaint. 10 of the 14 patients were sigmoidoscoped, mostly by Mr. E. Tuckwell. 6 of these, including the 2 patients with diarrhœa, showed a peculiar, pale, dry, rather rigid wall of the rectum and lower sigmoid colon which we regard as a characteristic appearance in the disease. All 6 patients had gross radiological changes in the colon and it is interesting to record that, of the remaining 4 whose sigmoidoscopies were normal, 2 showed radiological evidence of colon involvement.

Fig. 1 (*Case* 2).—A hand, showing limits of flexion and extension. The curled fingers are thick and tapered. Small ulcer. Telangiectases.

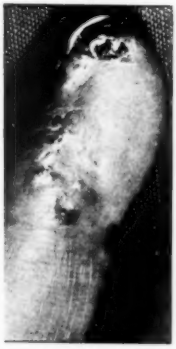


Fig. 2 (*Case* 3).—Ulcer at finger-tip.

Fig. 3 (*Case* 3).—Calcareous deposits near elbow. Telangiectases.

Manifestations Elsewhere in the Body

That many of the patients complained of fatigue is not surprising. 6 of them had marked loss of weight. Their menstrual history was uneventful. Slight anæmia was the rule.

How tempting it is at this point to discuss the probable much wider involvement of the body tissues by the disease process. Changes in the lungs and heart have been described in the literature and will be referred to by Dr. Kemp Harper, who will also speak of some interesting changes in the jaw. Renal lesions have been recorded and there are hints in the present cases of involvement of other organs such as the liver and spleen. 3 patients complained of unexplained frequency of micturition. One of these was cystoscoped by Mr. A. Badenoch who found a marked bullous formation on the whole of the trigone, and on the posterior wall of the bladder a curious condition of metaplasia which suggested malakoplakia. This type of lesion and many others need further study.

Course of the Disease

The course of the disease is exemplified by the following brief case abstracts of 4 of the patients:

(1) Miss E. G. (Case 7). Aged 44. First noticed symptoms of Raynaud's phenomenon in the hands at the age of 27. During the next thirteen years these symptoms became increasingly tiresome, and at the age of 40 she had a bilateral sympathectomy performed. Far from relieving the condition, the operation was followed by thickening and stiffening of the skin of the hands and, later, of the face. Three and a half years after the operation, and three months before I saw her, she began to have pain in the left lower quadrant of the abdomen, loose stools passed up to fourteen times a day and occasional vomiting. The symptoms persisted and she lost one and a half stones in weight in the next three months.

On examination, typical changes of scleroderma were seen in the hands, forearms, face and upper chest; and to a lesser extent in the feet and legs below the knees. There was radiological evidence of digital calcification and phalangeal absorption in the fingers.

The stools were only semi-formed and the colour of putty.

X-rays taken after a barium swallow showed the typical changes in the œsophagus (to be described by Dr. Kemp Harper); in this instance there was a diminution of peristalsis, most marked in the lower third, resulting in barium remaining a long time in the œsophagus when the patient lay on her back.

Sigmoidoscopy revealed a peculiar pale, dry, rather rigid wall of the rectum and lower sigmoid colon.

X-rays after a barium enema demonstrated the classic large diverticula of the colon (*see* Fig. 14, p. 519).

Following symptomatic treatment with a low residue, high calorie diet and methyl ethyl cellulose the bowel actions became less frequent, vomiting ceased and the patient gained 6 lb. in weight during her six weeks' stay in hospital. She was also given tocopherol, 400 mg. daily, and it was thought that her face improved.

(2) Mrs. D. B. (Case 2). Aged 33. First noticed symptoms of Raynaud's phenomenon in her hands at the age of 23. One year later, the backs of both her hands became swollen and the skin tense and shiny. The movement of the fingers was impaired. Three years after, at the age of 27, when the condition had worsened, she had a bilateral cervical sympathectomy, without relief. At the age of 29, she began to have attacks of numbness and coldness in the feet and, some months later, stiffness of the feet. One year after this she had an attack of herpes zoster on the right side of the thorax and she found later that a fibrous band formed in the skin along the line where the vesicles had been. At the age of 31, small recurrent ulcers appeared on both legs and a red macular rash on the face. At about this time her dentist remarked on the stiffness of her mouth. One year later, eight months before I saw her, she developed gangrene of the 3rd left toe which improved by treatment with Priscol.

On examination, there were sclerodermatous changes in the hands, forearms, face, thorax, and to a lesser extent in the feet and legs.

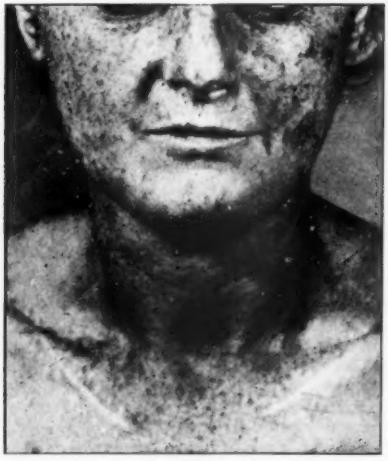


FIG. 4 (*Case* 2).—Tight skin of face and neck. Small mouth. Telangiectases. Scars of bilateral cervical sympathectomy.

The skin over the forearms and hands was thickened and shiny. Extension of the fingers, which were tapered and showed small ulcers and telangiectases, was grossly limited, and the hands were held in a position of slight flexion with the fingers curled (*see* Fig. 1). X-ray showed digital calcification and phalangeal absorption.

The skin of the face was tight and somewhat atrophic. There was loss of mobility of the skin and, consequently, of normal facial expression. The mouth was small and could not be fully opened. There were telangiectases on the forehead and cheeks (*see* Fig. 4).

The most interesting skin change in this patient was a white, tough, fibrous band 8 in. long and ¼ in. wide on the lateral aspect of the right side of the thorax, at the site of the herpes zoster which she had had three years previously.

This patient complained of no gastro-intestinal symptoms except for constipation, but the radiological appearances of the œsophagus and the colon were the same as those described in the first case. Identical sigmoidoscopic changes were also seen, but these were confined to the lower two-thirds of the rectum.

Treatment with ACTH led to increased movements of the fingers and hands and some lessening of the tightness of the skin. Sad to relate, when the treatment was stopped the improvement was not maintained.

(3) Mrs. L. W. (Case 10). Aged 65. Had had chilblains of the fingers since early childhood. Not until her menopause at the age of 50 did she first notice symptoms of Raynaud's phenomenon in the fingers. When she was aged 54 she had a partial gastrectomy because she had a gastric ulcer and an hour-glass stomach. Following this operation, diarrhœa began with six loose stools a day, and was still present ten years later when I first saw her. At the age of 64 her fingers had become much worse and the right index finger was swollen and ulcerated. She had a bilateral cervical sympathectomy. After that she felt more ill. Food stuck at the bottom of her gullet and was often returned; the symptoms were worse with solids than with liquids. There was anorexia, retching and flatulence. The diarrhœa continued. She lost weight. Her legs began to swell.

On examination, one year after the sympathectomy, the sclerodermatous changes were prominent in the hands, upper back and legs. During her stay in hospital similar changes became apparent in the face. X-rays showed not only the characteristic changes in the œsophagus and colon, but also in the small intestine. The sigmoidoscopic appearances were identical with those seen in the 2 cases already described above.

Gradually her condition deteriorated and she died two months later with bronchopneumonia.

(4) Mrs. M. W. (Case 14). Aged 33. First noticed symptoms of Raynaud's phenomenon in her hands at the age of 23. Later her feet became affected also, but to a lesser degree. At the age of 31, the symptoms in her hands were worse and the fingers ulcerating. She had a bilateral sympathectomy. Shortly after this the skin on the backs of her hands, face and feet became tight, stiff and shiny.

At the age of 32 she had difficulty in swallowing solid food. Her weight decreased. All her other symptoms became worse and she found herself short of breath on exertion.

On examination, she was dyspnœic and dysphagic, with a husky voice. There was gross scleroderma of the hands, forearms, upper trunk, face, feet and legs. There was a pleural effusion on the left side.

When X-rays of the œsophagus were taken she experienced great difficulty in swallowing a thin suspension of barium. Some of the barium was seen to spill over into the larynx, which caused a severe bout of coughing. The barium then passed slowly down the œsophagus and pooled in the lower half, where peristalsis was much diminished.

The colon was normal radiologically and no abnormal changes were seen through the sigmoidoscope.

Laryngoscopy showed poor adduction of the vocal cords, which failed to abduct on deep inspiration. There was a large amount of frothy mucus in the pyriform fossae. Pharyngoscopy showed a fibrous stricture at the level of the cricopharyngeus muscle, and this was dilated with bougies.

Œsophagoscopy was difficult, as it so often is in this disease (Bourne, 1949), but the upper 9 in. looked normal.

Two days later, the patient, who had been becoming rapidly more dyspnœic and more dysphagic during her short stay in hospital, had melæna and acute dyspnœa, and died.

Treatment

This is not the place to discuss the many treatments from vitamins to cortisone which have been tried on these cases, or on others described in the literature. Suffice it to say that whereas some treatments have seemed temporarily beneficial, none has been curative. It is important to note that 6 of the 14 patients here described had had cervical sympathectomy for Raynaud's phenomenon of the hands and 2 of the 6 had also had lumbar sympathectomy for Raynaud's phenomenon of the feet. In no instance did the operation arrest or appear to delay the development of the disease; an experience which is in accord with that of other observers such as Truelove and Whyte (1951).

Prognosis

Diffuse systemic sclerosis is a disease of slow development and long duration. 10 of the 14 patients had had symptoms for ten years or more, 2 for twenty years. It is possible that the disease sometimes becomes arrested, although there is no evidence of this happening in the present cases. No treatment has yet been found which cures or even stays the disease process. Until it has, it would seem that the most likely course of diffuse systemic sclerosis is a slow but inexorable worsening, probably ending in death. 4 of the 14 patients are dead; 1, fifteen years after the onset of symptoms, from bronchopneumonia; 2, ten years after, from hæmorrhage; and 1, two years from the beginning, from no obvious cause.

Epilogue

The relationship of dermatomyositis to diffuse systemic sclerosis is uncertain. It may possibly be a manifestation of it. Involvement of skeletal muscles in scleroderma was described in the last century by Addison (1868). However, the subject is discussed by Brock (1934) in a review of the entire literature to that time, and he believes the diseases are two separate entities. Otherwise the diagnosis is not difficult.

The clinical features are so similar in these 14 cases that one is justified in regarding the condition as a distinct disease entity. In considering a suitable title, the terms scleroderma, acrosclerosis and sclerodactyly are inadequate. They do not connote the widespread involvement of the body by the disease process, how widespread we do not yet know. Until we know more of the essential nature of the disease, the most useful title would seem to be that proposed by Goetz (1945): " Diffuse systemic sclerosis."

REFERENCES

Addison, T. (1868) Collected Edition. *New Sydenham Society*, **36**, 177.

Basch, M. C. (1932) Thesis. Paris.

Bourne, W. A. (1947) *Proc. R. Soc. Med.*, **40**, 463.

—— (1948) *Proc. R. Soc. Med.*, **41**, 43.

—— (1949) *Lancet*, i, 392.

Brock, W. G. (1934) *Arch. Derm. Syph., Chicago*, **30**, 227.

Ehrman, S. (1903) *Wien. med. Wschr.*, **53**, 1097, 1156.

Garcin, R., Bertrand, I., Laudat, M., and Cachin, C. (1931) *Bull. Soc. méd. Hôp. Paris*, **47**, 1036.

Goetz, R. H. (1945) *Clin. Proc., Cape Town*, **4**, 337.

——, and Rous, M. C. (1942) *Clin. Proc., Cape Town*, **1**, 244.

Hutchinson, J. (1896) *Clin. J.*, **7**, 240.

Littler, T. R., and Canter, S. (1951) *Lancet*, i, 139.

O'Leary, P. A. (1943) *Canad. med. Ass. J.*, **48**, 410.

——, and Waisman, M. (1943) *Arch. Derm. Syph., Chicago*, **47**, 382.

Prowse, C. B. (1951) *Lancet*, i, 989.

Ramsey, A. S. (1951) *Brit. med. J.*, ii, 877.

Raynaud, A. G. M. (1862) De l'asphyxie locale, et de la gangrène symmétrique des extremities. Paris. (Selected Monographs. *New Sydenham Society*. Vol. **121**, 1, 1888.)

Sellei, J. (1931) *Arch. Derm. Syph. Wien.*, **163**, 343.

—— (1932) *Münch. med. Wschr.*, **79**, 1625.

Thibierge, G., and Weissenbach, A. J. (1910) *Bull. Soc. méd. Hôp. Paris*, **30**, 10.

Truelove, S. C., and Whyte, H. M. (1951) *Brit. med. J.*, ii, 873.

Weber, H. (1897) *KorrespBl. schweiz. Ärz.*, **8**, 623.

Weissenbach, R. J., Boppe, Hoesli, H., Martineau, J., and Malinsky, A. (1935) *Bull. Soc. franç. Derm. Syph.*, **42**, 1412.

Dr. R. A. Kemp Harper, Director of Diagnostic Radiology Department, Saint Bartholomew's Hospital, London:

The Radiological Manifestations of Diffuse Systemic Sclerosis (Scleroderma)

THE purpose of this investigation was to examine extensively a number of patients suffering from scleroderma, and to assess the frequency of the changes previously reported; also to investigate more thoroughly the alimentary manifestations of the disease. This was carried out in collaboration with Dr. E. R. Cullinan, who undertook the clinical assessment of these patients.

The patients were in varying degrees of ill-health, and this accounts for the fact that each patient could not be subjected to the full investigation desired, and for the slight variation in the number of examinations of each system as seen in Table I.

TABLE I

	Age	Duration of symptoms in years	Digital calcifn.	Phalangeal absorption	Other soft tissue calcifn.	Alimentary symptoms	Œsophagus	Small intest.	Colon	Heart	Lungs
1 M. B.	71	10	–	–	Wrist	–	+	–	+	+	+
2 D. B.	33	10	+	+	–	–	+	N.E.	+	–	–
3 G. C.	67	20	+	+	Elbows	–	+	–	–	N.E.	N.E.
4 E. C.	49	20	+	+	–	+	+	–	+	–	–
5 F. C.	51	2	–	+	–	–	+	N.E.	N.E.	–	?
6 H. C.	56	1	+	+	–	+	+	N.E.	N.E.	–	–
7 E. G.	44	17	+	+	–	+	+	–	+	–	–
8 S. G.	46	11	+	+	–	+	+	?	+	–	–
9 W. L.	38	8	–	+	N.E.	–	+	Duod	+	–	–
10 L. W.	65	15	N.E.	N.E.	N.E.	+	+	+	+	–	Eff.
11 G. W.	43	6	+	+	Buttocks ? parotid	+	+	–	–	+	–
12 K. W.	45	15	N.E.	N.E.	N.E.	+	+	+	+	+	+
13 H. W.	39	10	–	+	N.E.	–	+	–	–	+	–
14 M. W.	33	10	N.E.	N.E.	N.E.	+	+	N.E.	N.E.	N.E.	N.E.
	49 (Average)	11 (Average)	7/11	10/11	3/9	8/14	14/14	3/10	8/11	4/12	4/12

(N.E. = not examined)

There have been many accounts of radiological changes in scleroderma, most of which have referred to alterations seen in only one system or part of the body; in only two articles have attempts been made to describe extensive radiological changes in this condition. In 1943, Jackman described the changes then known to occur in this disease, but little was known about the alimentary tract at that time, apart from certain features in the œsophagus.

In 1931, Rake described dilatation of the small and large intestine, seen at autopsy; there was no indication of obstruction. In 1944, Hale and Schatzki described their findings in the alimentary tracts of 22 patients whom they examined radiologically. This was the first authoritative account of widespread changes in the alimentary tract. In addition to œsophageal changes, they described dilatation of loops of the small intestine, but did not ascribe a cause for this. They found saccular dilatations of the colon in 2 patients, and in 1 of these there were also areas of rigidity similar to those seen in ulcerative colitis. They suggested that the colonic changes might be due to scleroderma, but that the evidence was not convincing, although in view of negative sigmoidoscopic findings in the second case, scleroderma might be the cause.

I propose to show that these changes which we have confirmed in our own patients are, in fact, part of the picture of scleroderma as it affects the alimentary tract.

THE SOFT TISSUE AND BONY CHANGES IN SCLERODERMA

Conditions such as leprosy, Buerger's disease, lupus erythematosus, diabetes mellitus, frostbite and ainhum and others, produce absorption of the terminal phalanges of the hands, and sometimes of the feet, but, apart from Raynaud's disease, no other condition appears to produce the association of absorption and calcinosis, and further investigation indicates that such cases of Raynaud's disease with calcinosis are usually suffering from scleroderma.

Calcification occurs chiefly in the fingers, often on the palmar aspects of the terminal phalanges, and 7 out of 11 patients examined showed digital calcification, but it may also be found in the hands, in the elbows, buttocks, shoulders and also in the legs. Pollitzer (1918) has even recorded calcification in the face of a patient in areas affected by scleroderma. Calcification can occur in areas of soft tissues without overlying skin changes of a sclerodermatous nature, and the degree and distribution of calcification may vary from time to time, as shown by Scholz (1932) who argued that the connective

tissues were pathological, although the overlying skin had not yet been affected. The calcinosis may be seen in any type of the disease, and can be differentiated from types of metastatic calcification by the presence of other features of scleroderma. Scholz suggested that it might be called dystrophic calcification as compared with the metastatic form.

The bony changes seen are, in the main, absorption of the tufts of the terminal phalanges due to diminished vascular supply (Fig. 1) but the absorption may be extensive and involve middle or even proximal phalanges. We have found varying degrees of absorption in 10 out of 11 patients.

The absorption seems to commence on the palmar aspects of the tufts of the terminal phalanges, and lateral views are important in recognizing the earliest changes. The process continues until extensive erosion may result. Accompanying calcification of the soft tissues may be missed in the early stages, unless lateral films of the individual fingers are taken. A curious feature to be noted is the coincidence in certain cases of dense stippling of the terminal phalanges. This stippling may be simulated by calcification in the soft tissues, and this is a further reason for the use of lateral projections. It is interesting that all three appearances may be seen together in one patient, and their association was first described by Edeiken in 1929. The intra-osseous calcification was also commented on by Podkaminsky in 1937.

The disease often includes the presence of arthritic changes, and the loss of mobility which ensues probably accounts in part for the widespread osteoporosis which may be seen in these cases (Fig. 2). Subluxation and dislocation may also be features from the combined effect of absorption and arthropathy.

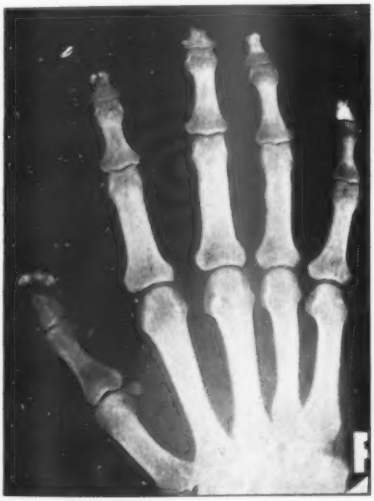


FIG. 1 (*Case* 7).—Extensive absorption of all terminal phalanges. Sclerosis of the remaining portions of some the phalanges and considerable soft tissue calcification.

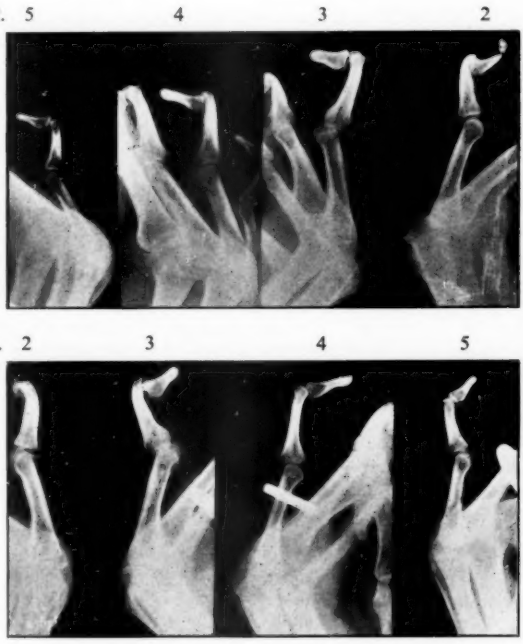


FIG. 2 (*Case* 11).—Acute flexion of fingers, varying degrees of absorption and arthritis. Some phalangeal sclerosis and slight soft tissue calcification. Dislocation and subluxation of terminal phalanges. The subluxations are associated with absorption of the palmar aspects of the heads of the intermediate phalanges. Few of these changes were discernible on the A.P. film.

The other sites of calcium deposition are mainly in the pressure areas, i.e. elbows and buttocks (Figs. 3 and 4). The deposits may be very fine and discrete, but can become extremely dense. We have one instance of calcification in a parotid gland, but it is a little difficult to be sure that this is the result of the sclerodermatous process, as repeated attacks of parotitis have occurred.

Jackman (1943) suggests that there is a lowering of CO_2 concentration in the devitalized tissues as a result of lowered metabolism. The reaction becomes alkaline, and lime salts are precipitated from blood and lymph which diffuse into the area. It seems likely, however, that devitalization of all the tissues is required as in scleroderma before the absorption and calcification are seen together, the disease obviously affecting all the mesenchymal tissues.

Stafne and Austin (1944) in the course of their dental work found that 10% of patients suffering from this disease had definite changes to be seen on dental X-ray examination. This was indicated by the presence of a wide translucent zone round the roots of the teeth like a widened periodontal space, and was found to represent a thickened and fibrous periodontal membrane. The dense alveolar line (lamina dura) surrounding this remains intact, or reappears after a time if absorption takes place. The changes seem to be characteristic of this disease, and although the teeth might appear to be loose, they are usually still firmly fixed in the jaw. We have found that in some cases the roots assume a slightly tapered shape resulting also from some absorption of the apices (Fig. 5). We have only been able to examine 2 patients for this feature and both were positive.

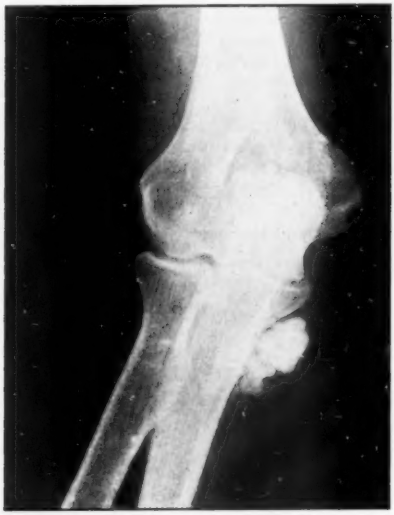


FIG. 3 (*Case* 3).—Amorphous calcification in region of elbow.

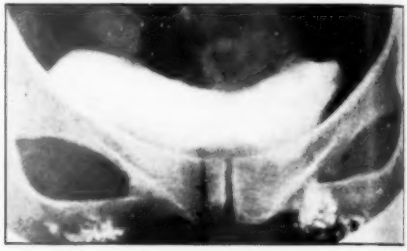


FIG. 4 (*Case* 11).—Calcification in close relation to both ischial tuberosities.

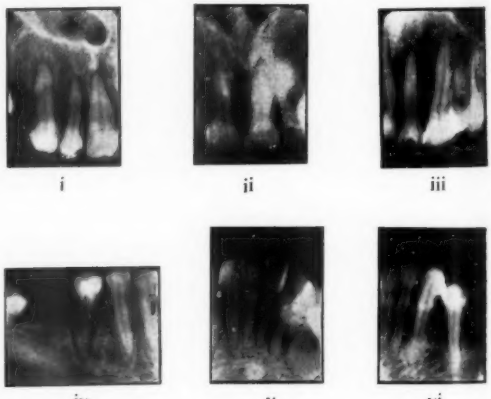


FIG. 5 (*Case* 7).—Even widening of several of the periodontal spaces, but lamina dura still present in most instances. This seems to be a pathognomonic feature of scleroderma.

PULMONARY CHANGES

These seem to occur only in the more severe generalized cases of scleroderma, and result in gradually increasing dyspnœa. The changes are a combination of fibrosis and cyst formation.

Von Notthafft (1898), Matsui (1924), and Kraus (1924) have reported a total of 6 cases with pulmonary fibrosis on pathological examination. Matsui also drew attention to the occurrence of changes in the lesser circulation, resulting in right ventricular hypertrophy.

Attention was again drawn to the pathological features by Getzowa in 1945. She described 2 cases seen at autopsy in which she found cysts of from pinhead size to 1·5 cm. in diameter. The hilar and apical areas were comparatively free, and they were most frequent in the paravertebral areas of the lungs. No large cysts were noted in either case. The alveolar walls were thickened due to marked congestion of the capillaries and to the presence of fibrosis.

The hyaline portions of the alveolar parenchyma had been dissolved, and the parenchyma was replaced by cystically enlarged bronchiolar proliferations, and extensive intra-alveolar fibrosis.

Bevans (1945) commented on the presence of extensive endarteritis of the pulmonary vessels in describing the changes found in the lungs in this disease.

Murphy, Krainin and Gerson (1941) claimed to be the first to give the radiological features of lung changes in scleroderma. They described the following case:

Female, aged 30. Changes in skin of face, arms, legs and feet. Complained of dyspnœa. There were diffuse network-like changes in the lungs. Sputum and bronchography were negative. A pneumothorax was induced to prove that the changes were intrapulmonary. In the hands, all the terminal phalanges were almost completely absorbed.

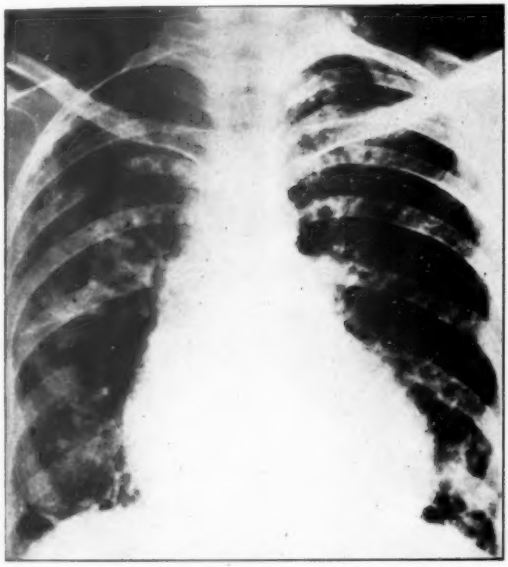


FIG. 6.—Enlarged heart, probably due to myocardial changes and pericardial effusion. Widespread lung changes found to be due to pulmonary fibrosis and very widespread small cystic changes. (Dr. W. S. Shearer's case.)

It is likely that some of the recurrent pneumonic episodes are caused by "spill-over" from the œsophagus where the latter is extensively affected.

Our own experience is that lung changes are only recognizable in the more advanced stages of the disease, and when they occur patients tend to have recurring episodes of patchy or localized pneumonitis or of pleurisy with effusion. Case 10 (Table I) has had frequent episodes which have necessitated repeated admissions to hospital.

Fig. 6 illustrates advanced disease of the lungs, which at autopsy presented a finely lobulated appearance from the presence of innumerable cysts; these varied from pinhead size to 2 cm., and the pericardial and both pleural sacs contained fluid. I am indebted to Dr. W. S. Shearer for the details and illustrations of this case.

Cardiac Changes

It is well known that the cardiac muscle may be equally affected by the widespread degenerative process, and this on occasion results in gradual enlargement of the cardiac silhouette, whilst fluoroscopy will show deficient cardiac pulsation. The element of pulmonary resistance to blood flow from the accompanying lung changes may result in right ventricular hypertrophy, and this also probably contributes to the enlargement. The cardiac manifestations have been admirably described by East and Oram (1947). Some of the enlargement is sometimes due to fluid, as the presence of fluid in the sac is a frequent finding at autopsy (Weiss, Stead, Warren and Bailey, 1943), and Bevans (1945) has also reported inflammatory changes in the pericardium at autopsy.

Changes in the Alimentary Tract

Œsophagus.—One patient has been seen in whom dysphagia was found, which resulted in spill-over into the trachea. This was found to be due to a stricture in the cricopharyngeal area, which could not, however, be unequivocally attributed to scleroderma, although it may be assumed to be, as Smitham (1952) has encountered this lesion in 2 patients. No other patient had any difficulties of this type, and no other example of this lesion has been described in the literature.

Lindsay, Templeton and Rothman (1943) reported 5 cases in which the changes in the œsophagus were variously interpreted as indicative of achalasia, œsophagitis, diverticulum or atony. They state that the outstanding feature is localized narrowing 4–5 cm. above the lower end of the œsophagus, with proximal dilatation. This narrowing has also been seen in some of our cases.

Johnstone (1948) mentions hiatus hernia as an occurrence in this disease, and we have seen it, although again not as a predominant feature. Bourne (1949) described in one of his cases the presence of chronic œsophageal stricture, which had been watched for several years. Histological changes in the œsophagus have been described by Rake (1931), Weissenbach *et al.* (1938), Kuré *et al.* (1936), Lindsay *et al.* (1943), and Bevans (1945). All describe erosions, thickening of submucosa and atrophy of the muscular coats, and Goetz (1945) states that in all his 3 cases which came to autopsy, ulceration was found.

On radiological examination, in the erect posture no change may be perceived on screening unless a stricture has occurred. The patient has to be examined in the recumbent posture, as only then

may the absence of peristalsis be observed. This is the outstanding feature, and in obvious cases is very marked. Yet the patient may have very little dysphagia, and the changes may be noted without the patient complaining of any discomfort, although a leading question may elicit some history of discomfort behind the sternum.

In the earlier stage of the disease, peristaltic waves may be seen in the upper and sometimes middle third of the œsophagus, which travel for a varying distance down the viscus, but fade out before reaching the lower end and completing the task embarked upon. This may be followed by many small tertiary contractions and then by atony. A curious cobblestone pattern in the mucosa has also been seen in several cases, and these probably represent leucoplakia in the mucosal coat, as has sometimes been found at autopsy (Fig. 7).

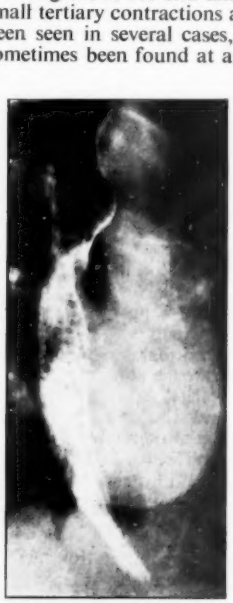


FIG. 7 (*Case* 8.)—Cobblestone appearance in the œsophagus resulting from leucoplakia. Inert œsophagus.

FIG. 8 (*Case* 2).—Deformity of lower end of œsophagus from irregular stricture formation.

FIG. 9 (*Case* 6).—Dilated atonic œsophagus. Short œsophagus and hiatus hernia.

In severe cases, one sees a completely inert mass of barium remain in the lower half of the œsophagus, but some patients exhibit certain feeble and incomplete attempts at peristalsis or tertiary contractions, which do not alter the amount of opaque material in the gullet.

It seems highly probable that a variety of conditions may occur at the lower end. Spasm as described by Goetz, stricture as illustrated by Bourne (Fig. 8), achalasia from a low stricture, ulcer following regurgitation described also by Goetz, and hiatus hernia (Fig. 9). The stricture seems to occur at any point in the lower third of the œsophagus, and varies in severity, but is seen usually above the site of election of cardiospasm. Absence of peristalsis, may however, prevent adequate examination of the narrow area, and so render unsatisfactory any attempt to study the precise details of the changes present. This is indeed one of the main difficulties encountered in endeavouring to arrive at a precise diagnosis, and, in addition, œsophagoscopy is oft-times impossible because of the fibrotic changes in the mouth and pharynx.

It has been suggested that the inflamed mucosa sometimes seen at œsophagoscopy is always secondary to reflux, as such changes do not occur in the buccal and pharyngeal mucosa; but, as we shall see later, similar changes may be seen in the colon, where a similar mechanism cannot be invoked, so that inflammatory changes may occur as part of the sclerodermatous process, without the additional factor of reflux.

Olsen, O'Leary and Kirklin (1945) have stated that 10% of patients with scleroderma and acrosclerosis had symptoms of dysphagia and also frequently retrosternal burning pain on lying down. They found positive endoscopic or X-ray findings in 18 patients. In 7, dilatation similar to cardiospasm was found, and hiatus hernia in 9 cases, of which 6 had short œsophagus. Olsen and Harrington (1948) reviewed 220 cases of hiatus hernia, and of these 10% had short œsophagus. Of these 22 cases, 9 were patients with scleroderma. This seems a very high proportion, and a striking figure, to which I feel attention should be drawn, as it is unlikely to reflect the findings in this country.

Barium may remain in the œsophagus for hours if the patient is left in the recumbent posture, unless regurgitation or vomiting occurs, as it is apt to do, especially in advanced disease.

In our series of 14 cases, all exhibited œsophageal changes consisting primarily of loss of peristalsis, which is the outstanding feature to be looked for, the other changes being secondary. In addition, 7 had strictures or spasm, 2 had hernia in addition, and 7 showed only peristaltic loss.

Stomach

This does not as a rule show changes like those observed in the œsophagus, peristalsis being well exhibited, but if the disease is advanced, changes may occur, as seen in the patient who had a partial gastrectomy years ago, and eventually developed very severe disease (Fig. 10).

Duodenum

The duodenum is more likely to show changes, which usually take the form of a mild ileus with its usual appearances. This has been observed in several patients (Fig. 11).

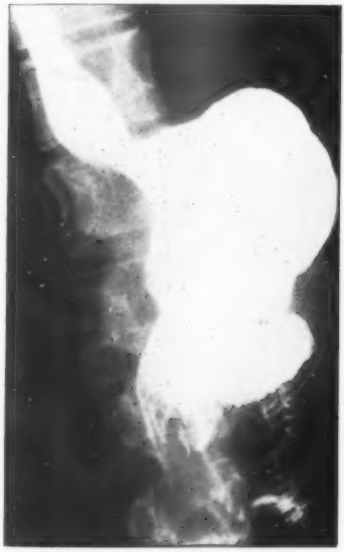


Fig. 10 (*Case* 10).—Inert œsophagus. Hiatus hernia, and atonic stomach. (Patient recumbent.) This patient had a gastro-enterostomy many years previously (*see* also Figs. 12 and 13).

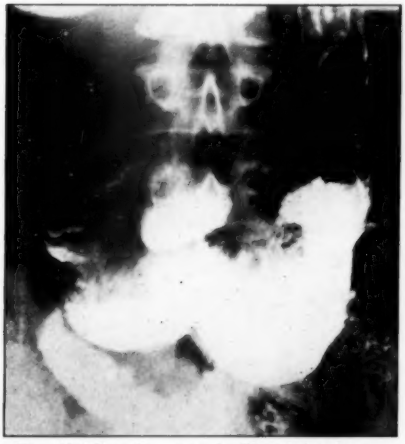


Fig. 11 (*Case* 9).—Atonic dilated duodenum.

Small Intestine

Hale and Schatzki in reporting 4 cases with alimentary changes found it involved in each instance.

Javier (1951) examined 8 patients with generalized scleroderma. He reported dilatation of the œsophagus, stomach and small intestine and, further, that the small intestinal lesions were striking. A decrease of the peristaltic movements was a constant finding.

We have conducted careful and frequent serial examinations of the small intestines, but have not found such a high incidence of changes in this area. 3 patients showed positive appearances out of 10 examined. There is delay of motility to a greater or lesser degree, and, additionally, one may demonstrate out-pouchings from the wall of the bowel, which represent diverticula formed when the muscular coat disappears in a patchy manner, as we have been able to demonstrate in both small and large intestines, and which was confirmed at autopsy (*see* Case 10, Fig. 12).

Again, in severe cases, barium may remain in the small intestine for upwards of forty-eight hours, these patients usually having symptoms of obstruction. One of Hale and Schatzki's cases was

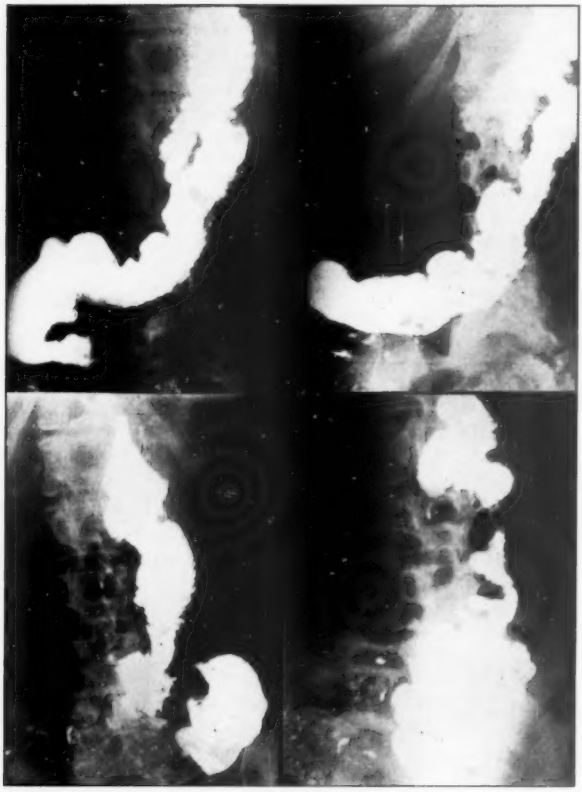


FIG. 12.

FIG. 12 (*Case* 10). — Inert stomach, much dilated jejunum immediately below the anastomosis. Films taken at two, four, six and eight hours. The proximal loop shows pouches which are more easily demonstrated in the colon.

FIG. 13 (*Case* 10). — Scattered residues throughout the small intestine after twenty-four hours. Large colonic pouches visible. Still small intestinal residues at forty-eight hours and much gaseous distension. Colonic pouches again seen.

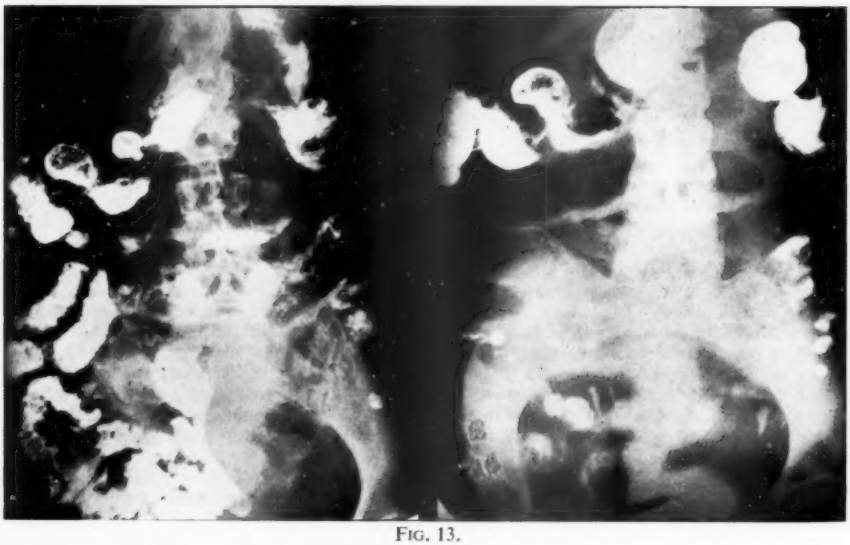


FIG. 13.

operated upon, and the obstruction relieved by resection, but it soon recurred, and operation is a very temporary palliative in what is really a widespread disease (Fig. 13).

Colon

This is often affected, and indeed we have found it easier to demonstrate changes in the large than the small bowel, 8 patients out of 11 examined showing definite changes.

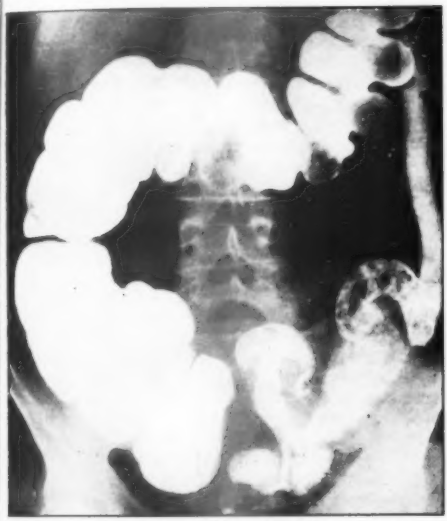


Fig. 14 (*Case* 7).—Large diverticula visible on ante-mesenteric surface of transverse colon. The descending colon presents features suggestive of ulcerative colitis. (Post-evacuation enema film.)

A barium serial examination may show an asymmetrical colonic outline with haustration on one side of the bowel, and a wide-mouthed diverticulum opposite the haustral indentation. This asymmetry may be quite striking, and, when large, these diverticula contain inspissated masses of fæces into which barium does not penetrate (Fig. 14). They may, however, be removed during preparation for a barium enema; if so, they fill well and produce an obvious bulge on one side of the bowel on filling the colon with barium, whilst the effect of the tannic acid enema is often spectacular, the pouches remaining uncontracted and filled with barium after evacuation, whilst the rest of the bowel contracts well (Figs. 15 and 16). These changes may be found in patients who have no symptoms of bowel trouble, but if the changes are marked, there is usually a history of alternating constipation and diarrhœa.

Although Bevans in her autopsies did not confirm the presence of narrowings of the large bowel, Goetz found several narrow areas in his 3 autopsies. In our own 2 autopsy cases, we found no strictures in the colon, although marked pouching was seen.

We have also observed a patient with severe disease, who showed changes in the descending colon which looked like ulcerative colitis, and

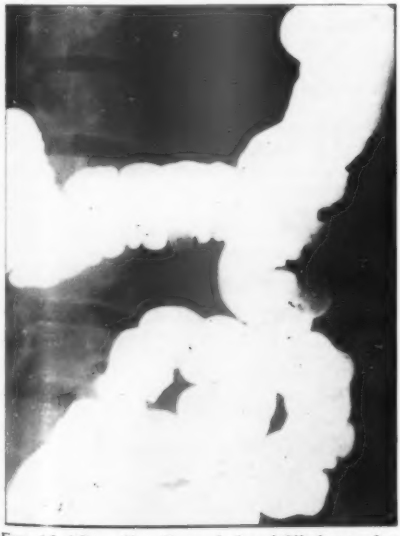


Fig. 15 (*Case* 2).—Several fæcal-filled pouches seen in transverse and descending colon.

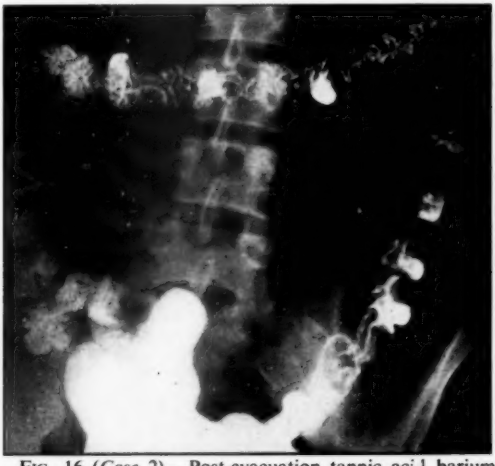


Fig. 16 (*Case* 2).—Post-evacuation tannic acid barium enema film. Most of the colon is empty except for barium retained in non-contractile pouches in transverse and descending colon. These pouches are the results of patchy absorption of the muscular coat of the colon, and appear to occur only in scleroderma.

were very similar to those seen by Hale and Schatzki in one of their cases, but which were not ascribed by them to scleroderma. There is no autopsy report available in this case, but there was no clinical evidence of ulcerative colitis, and the typical, rather grey, sclerodermatous mucosa was seen on sigmoidoscopy.

With such definite changes in the alimentary tract, it is obvious that these are variations of scleroderma and part of a generalized disease, which accords with Goetz' assertion of a systemic disease affecting all mesenchymal tissues.

Pathology

The pathological features of the alimentary changes are loss of muscle, thickening of submucosa and infiltration with leucocytes and plasma cells, and, in general, hypertrophy of the connective tissues.

A striking feature of the autopsy is the grey, slate-like glistening colour of the peritoneal surface of the intestines, and the peritoneum exhibits inflammatory changes on pathological examination.

In advanced disease, the bowel may, when held up to the light, appear almost translucent in the areas where the musculature has disappeared. As raw, exfoliated areas have been described in the œsophagus on œsophagoscopy, it is likely that similar changes occur in the colon and produce the unusual features which simulate ulcerative colitis.

Bevans has described the pathological features of the gastro-intestinal tract, and on section of the œsophagus she found the mucosa replaced by fibrillar acellular tissue. The muscle was replaced largely by fibrous tissue, but she regarded the Auerbach's plexuses as being intact. This is interesting, as certain writers, including Goetz, have explained the loss of œsophageal function on the basis of degeneration of these plexuses.

It is almost certain, however, that the change in and ultimate replacement of the muscle layers are sufficient to explain the gross alteration of function in the later stages, although it cannot be denied that changes in the nerve plexuses may also play a part.

Bevans suggests that the narrowing sometimes seen at the lower end of the œsophagus is mainly spastic, but strictures through which an endoscope would not pass have been reported, and it is certain that fibrous strictures occur, some from ulcers, healed or active, and others from fibrous replacement of the muscular coat. Elsewhere in the gastro-intestinal tract the changes are similar, and in many areas the mucosa and serosa are in close contact, where areas of muscular coat have completely disappeared.

This is the pathological explanation for the alimentary changes, and for the features which may be seen in the small, but more especially in the large, intestine.

I hope that the changes described have served to show that this disease process, which we are calling progressive systemic sclerosis as advocated by Goetz, produces gross lesions capable of radiological demonstration, and that radiology can contribute greatly to the diagnosis and assessment of the extent of this disease.

Conclusions

This investigation into the features of Diffuse Systemic Sclerosis which may be demonstrated by radiological examination, proves that the changes are often more widespread than may be realized clinically.

The fingers and the alimentary tract are the most frequent sites of pathological changes, but the alveoli may also show characteristic appearances, and at a later stage of the disease the heart and lungs are also sometimes affected.

Whereas the changes in the fingers have been extensively described before, the changes found in the colon have only been commented on once before by Hale and Schatzki. They were not sure that the features seen could be definitely ascribed to this disease, and erroneously regarded the areas of sacculation to be seen as areas of normal haustration with stricture formation between them. In fact, the reverse is the true state of affairs, with the colon generally of normal lumen, but with areas of sacculation or pseudo-diverticulum formation in various parts of the colon which are produced by the disappearance in patchy fashion of areas of the muscular coat. These are the hitherto unrecognized changes which have emerged from this investigation, but it is probable that there are others in the urinary tract which have yet to be elucidated.

It is hoped that the features described in this disease serve to justify our advocacy of the term "Diffuse Systemic Sclerosis", as propounded by Goetz, in preference to the present term of Scleroderma.

Summary

A series of patients suffering from "scleroderma" has been investigated radiologically and widespread changes were demonstrated.

These are best seen in the digits and alimentary tract, especially in the œsophagus and colon. Other features occur in the lungs, heart, alveolus, and in various soft tissue sites.

The changes are described and their frequency assessed.

I acknowledge with gratitude the fullest co-operation given by Dr. E. R. Cullinan, and many other of my colleagues in St. Bartholomew's Hospital during this investigation.

BIBLIOGRAPHY

ARONSON, S. M., and WALLENSTEIN, L. (1950) *N.Y. St. J. Med.*, **50**, 2723.
BEVANS, M. (1945) *Amer. J. Path.*, **21**, 25.
BOURNE, W. A. (1949) *Lancet*, i, 392.
DOWLING, G. B. (1940) *Brit. J. Derm.*, **52**, 242.
DURHAM, R. H. (1928) *Arch. intern. Med.*, **42**, 467.
EAST, T., and ORAM, S. (1947) *Brit. Heart J.*, **9**, 167.
EDEIKEN, L. (1929) *Amer. J. Roentgenol.*, **22**, 42.
GETZOWA, S. (1945) *Arch. Path.*, **40**, 99.
GOETZ, R. A. (1945) *Clin. Proc., Cape Town*, **4**, 337.
HALE, C. H., and SCHATZKI, R. (1944) *Amer. J. Roentgenol.*, **51**, 407.
JACKMAN, J. (1943) *Radiology*, **40**, 163.
JAVIER, R. G. (1951) *Ann. intern. Med.*, **34**, 862.
JOHNSTONE, A. S. (1948) Textbook of X-ray Diagnosis (Editors: Shanks, S. C., and Kerley, P. J.). 2nd Ed., 3, 53, London.
KRAUS, E. J. (1924) *Virchow's Arch.*, **253**, 710.
KURÉ, K., YAMAGATA, K., TSUKADA., S., and HIYOSHI, J. (1936) *Klin. Wschr.*, **15**, 516.
LANGMEAD, F. S. (1923) *Arch. Pediat.*, **40**, 112.
LINDSAY, R. J., TEMPLETON, F. E., and ROTHMAN, S. (1943) *J. Amer. med. Ass.*, **123**, 745.
LINGLEY, J. R., and ELLIOTT, W. J. (1941) Diagnostic Roentgenology, **2**, 1108, New York.
MATSUI, S. (1924) *Mitt. med. Fak. Tokyo*, **31**, 55.
MURPHY, J. R., KRAININ, P., and GERSON, M. J. (1941) *J. Amer. med. Ass.*, **116**, 499.
OCHSNER, A., and DEBAKEY, M. (1939) *Med. surg. J.*, **92**, 24.
O'LEARY, P. A., and WAISMAN, M. (1940) *Proc. Mayo Clin.*, **15**, 702.
——, —— (1943) *Arch. Derm. Syph., Chicago*, **47**, 382.
—— (1943) *Canad. med. Ass. J.*, **48**, 410.
OLSEN, A. M., and HARRINGTON, S. W. (1948) *J. thorac. Surg.*, **17**, 189.
——, O'LEARY, P. A., and KIRKLIN, B. R. (1945) *Arch. intern. Med.*, **76**, 189.
OLSON, G. M. (1917) *J. cutan. Dis.*, **35**, 96.
OTT, A. (1951) *Radiol. austriaca*, **4**, 201.
PODKAMINSKY, M. A. (1937) *Amer. J. Roentgenol.*, **38**, 889.
POLLITZER, S. (1918) *J. cutan. Dis.*, **36**, 271.
RAKE, G. (1931) *Bull. Johns Hopk. Hosp.*, **48**, 212.
RAMSEY, A. S. (1951) *Brit. med. J.*, ii, 877.
SCHOLZ, T. (1932) *Amer. J. Roentgenol.*, **28**, 92.
SMITHAM, J. H. (1952) Personal communication.
STAFNE, E. C., and AUSTIN, L. T. (1944) *Amer. J. Orthodont.*, **30**, 25.
THIBIERGE, G., and WEISSENBACH, R. J. (1911) *Ann. Derm. Syph., Paris*, **2**, 129.
TRUELOVE, S. C., and WHYTE, H. M. (1951) *Brit. med. J.*, ii, 873.
VON NOTTHAFFT, A. (1898) *Zbl. allg. Path. path. Anat.*, **9**, 870.
WEISS, S., STEAD, E. A., Jr., WARREN, J. V., and BAILEY, O. T. (1943) *Arch. intern. Med.*, **71**, 749.
WEISSENBACH, R. J., STEWARD, W. M., and HOESLI, H. (1938) *Ann. Derm. Syph., Paris*, **79**, 81, 198.

Dr. J. Hillyer Smitham: I have seen 8 cases of scleroderma with changes in the intestinal tract during the past two years. All of these showed some changes in the œsophagus, the most usual being lack of distensibility and loss of mucosal pattern. In 3 of the cases there were strictures in the œsophagus, 2 at the lower end about 2 in. above the cardia; in the third there were two strictures, 1 at the usual site and the other just above the level of the tracheal bifurcation.

I have been particularly struck by the similarity of the lung changes seen in this condition to those seen in cases of hiatus hernia with "spill-over" into the lungs. 4 of my cases showed such changes and of these 2 had œsophageal strictures and a third showed free reflux of barium into the œsophagus in the supine position.

The changes seen in the remainder of the gut consisted, in all cases, of a large duodenal bulb and several dilated coils of small gut with pseudo-strictures between them. These appearances are similar to those described by Ross Golden, in whose cases operation revealed dilated loops of small gut but no organic strictures and in which the histology of an excised portion of the dilated gut showed œdema only. The cases which I have seen complained of constipation rather than diarrhœa, and in one case the barium meal precipitated an attack of subacute intestinal obstruction which was eventually relieved by repeated colonic lavage.

Dr. G. Steiner (Manchester): The remark that changes in the lungs may occasionally result from overflow into the trachea due to muscular insufficiency of the diseased œsophagus should not be easily dismissed. A recently seen middle-aged man with a three-year history of scleroderma, in otherwise good general health, showed very marked œsophageal changes with complete loss of tone. There were not only multiple, often peribronchially arranged miliary-sized foci present in both lungs, but also a sizable abscess in the left lower lobe, without rise in temperature and very little symptoms. Sputum was persistently negative for tubercle bacilli.

Mr. P. R. Allison (Leeds): The incidence of œsophageal obstruction in patients with scleroderma or allied syndromes is obviously more than coincidental. The nature of the lesion, however, is more open to argument. The radiologists feel that they can suspect the diagnosis from their screening of the œsophagus, but I cannot do this, and I do not see in what way their films differ from those seen in reflux œsophagitis with stenosis complicating sliding hernia of the cardia. A sliding hernia can usually be demonstrated.

The appearance of the lesion through the œsophagoscope is identical with œsophageal peptic ulcer, and biopsies have never shown more than simple inflammatory tissue. The histological examination of the œsophagus removed at operation, where there has been no opportunity for the secondary digestion seen in the dead, has shown a lesion indistinguishable from peptic stenosis, with no trace of specific sclerodermatous changes. At operation a sliding hernia of the stomach is found and the changes occur in the œsophagus immediately above the cardia.

I feel, therefore, that we are entitled to say that the œsophageal obstruction in scleroderma is caused by peptic stenosis secondary to reflux œsophagitis, and that this is the result of a sliding hernia of the cardia through the diaphragmatic hiatus into the mediastinum. What happens in scleroderma to make the patient liable to these changes is not known. It could obviously be in the intrinsic or extrinsic mechanisms of the cardia or even in both.

In 2 patients on whom I have operated, the changes at the cardia were associated with chronic duodenal ulcer, and in one of these, pyloric stenosis was present, so that the stomach was becoming occluded at both ends. This association needs further investigation for it may be that changes at the pylorus lead to rigidity, prolapse of mucous membrane and secondary ulceration. These patients both showed the dilatation and laziness of the jejunum that have been described. At operation the wall looks and feels like damp thin cardboard, and it has a lumen more like that of the colon. As I normally use this part of the intestine for anastomosis to the œsophagus after resection of the cardia, I had an opportunity to remove a small portion for histology. This was put through the normal channels for pathological investigation so that no details about the thickness of the various layers were given, but the report indicated that this was normal small intestine. Is it possible therefore that the underlying trouble is a neuromuscular abnormality ?

Dr. W. A. Bourne: Both clinically and radiologically, the early manifestations of scleroderma must be regarded as functional rather than anatomical. Indeed, in 4 cases coming to post-mortem, lesions recognizable histologically as scleroderma have only been found in the myocardium of 1 and the small intestine of another. Disturbances of motility in the intestinal tract, like peripheral vascular disturbances in the hand, may precede detectable organic change by many years. Even when this is present it has not often been sclerodermatous, the œsophageal lesions—as workers in Leeds state—being the same as those in peptic ulceration. I believe this does, in fact, occur as a result of the failure of the œsophagus to maintain sufficient tone to overcome positive intra-gastric pressure, so that reflux of gastric contents occurs. Some organic change must be the basis of sclerodermatous process, but I do not think we can yet distinguish it in its early stages, and it must not be confused with the secondary effects of functional disturbance, whether gastro-intestinal or vasomotor.

Dr. E. Geddes Redman (University College Hospital, London): I have had an opportunity of seeing several patients in the Radiodiagnostic Department and have had access to the records of others.

In our series of 2 males and 6 females, the youngest was 20 years, and the oldest 60 years; they all exhibited some of the signs and symptoms described by Dr. Cullinan and Dr. Kemp Harper.

A patient with soft-tissue calcification in the hands and right elbow-joint region developed a pericardial effusion during convalescence following a gynæcological operation. This subsided eventually.

Another case, a female aged 51, was thought to have changes due to scleroderma in the œsophagus on fluoroscopy, but this was not confirmed at autopsy; she had marked involvement of the soft palate.

A very wide atonic duodenum was demonstrated in a female aged 37 years who had marked changes in the soft tissue and muscles and positive radiological findings in the lower end of the œsophagus, stomach and small intestine. Opaque medium was still present in the duodenum ninety-six hours after the meal had been given. I have not had the opportunity yet of seeing the changes which Dr. Kemp Harper has demonstrated in the colon.

United Services Section

President—Sir STANFORD CADE, K.B.E., C.B., F.R.C.S., M.R.C.P., Hon. F.F.R.

[*March* 5, 1953]

DISCUSSION ON SURVIVAL AND RESCUE

Wing Commander A. J. Barwood: *Emergency Escape and Survival*

Survival may be described as the ability of aircrew and passengers to tolerate any abnormal conditions to which they may be subjected during flight, during crash landing and ditching and after crash landing and ditching. These problems are intimately associated with the design of the aircraft.

There are three separate phases which may occur during an emergency. First there is the phase during which the aircrew and passengers will have to survive a period of extremely low barometric pressure subsequent upon failure of cabin pressurization system or perforation of a pressure cabin aircraft. Secondly, there is the stage in which aircrew would have to survive emergency abandonment of their aircraft either by normal parachute means or by the use of ejection seats and the subsequent free fall to a region of 10–12,000 feet and the separation from their seat and opening their parachute. Finally, there is the condition which may occur in any part of the globe on land or sea, in the Arctic, in the tropics, jungle or desert, of survival after the emergency.

It is highly desirable that aircrew should be able to tolerate explosive decompression which may occur as a result of structural failure of transparencies, mechanical failure of pressurizing systems or from enemy action in operational aircraft so that they can return to their bases with their aircraft and again be available as highly trained individuals to carry on the offensive. Man cannot cope effectively at altitudes in excess of 40,000 feet, even though he breathes pure oxygen, and as aircraft now operate at altitudes far in excess of that figure some alteration of oxygen equipment becomes necessary if aircrew are to be able to tolerate explosive decompression at altitudes in excess of 45,000 feet. Various schemes have been devised the oldest of which is the pressure breathing waistcoat. By the use of this equipment the oxygen pressure in the lungs is increased up to 12 in. of water pressure above ambient and aircrew are able to tolerate altitudes of up to 43,000 feet or are able to descend, as rapidly as the aircraft will permit, from an altitude of 47,000 feet to an altitude of 40,000 feet. It is essential to remain at as great an altitude as possible because reduction in altitude increases the amount of fuel required to cover a given distance by the aircraft, the amount of fuel being more or less inversely proportional to the air density. If the aircraft habitually flies at altitudes in excess of 47,000 feet it will be necessary to use some alternative pressurizing device such as a pressure suit which totally encloses the airman's body so that the entire body can be pressurized and maintained at the same altitude whatever the external altitude.

To enable aircrew to abandon the aircraft satisfactorily, various schemes have been devised. The pilots of the larger types of operational aircraft are equipped with ejection seats, but the crew members have static backward facing seats and if it becomes necessary to abandon the aircraft in flight the pilot controls it as best he can while these crew members abandon the aircraft through an emergency door or hatch which must be so placed that they will fall free of the aircraft and be able to descend safely by free fall to an altitude of 10–12,000 feet where their parachutes will be opened by an automatic barometric device. The pilots use their ejection seats which must clear the aircraft structure effectively and if the seat can be stabilized they may ride the seat down to a similar altitude where they will be automatically released from the seat and their parachutes will automatically develop. During the free fall emergency oxygen will be supplied to their normal oxygen mask which must be effectively retained to the helmet and a degree of protection from the extreme wind blast will be essential. The rate of acceleration of the seat during ejection is of extreme importance as too rapid a rise in the rate of acceleration is likely to cause structural damage to the body, and the seat pan must be relatively hard so that the body does not sink into it and then rapidly accelerate when compression of the seat substance is achieved. In the British type of ejection seat face protection during ejection into the slip stream is achieved by the use of a blind which is the firing mechanism of the seat.

If the aircraft is relatively intact and flyable it may have to be crash landed or to be ditched on the sea. In either of these conditions the rate of deceleration may be extremely rapid and it is necessary forcibly to retain the crew in their seats so that they cannot be flung out of their seats and killed or injured by impact with the aircraft structure. For this reason pilots are the only crew members seated in a forward facing position and they are supplied with an extremely strong and effective seat harness which will retain them effectively in their seat at decelerations of up to at least 25 *g*. Other crew members and passengers occupy backward facing seats, so that deceleration of their bodies whilst crash landing or ditching is taken by the seat behind them with adequate head support and little retaining harness is necessary except to eliminate lateral and vertical forces due to swinging and bouncing.

JUDY—UNIT. SERV. 1

The use of backward facing seats for passengers has effectively proven itself in several accidents which have occurred in the R.A.F. where aircraft have been subjected to a severe deceleration and rotation and passengers and crew members in backward facing seats have survived without injury whereas similar types of aircraft fitted with forward facing seats crash landing or ditching have had numerous casualties. The penalty of the backward facing seat is that the seat itself must be made strong enough to resist a 25 *g* deceleration of the occupant on it and a weight penalty is therefore incurred. In most types of aircraft a very much better view is obtained for the passenger with a backward facing seat and it cannot be too strongly recommended that it should be adopted by all civil airlines and they have been used for some years in the aircraft of the Royal Flight. All loose equipment carried in the aircraft must be capable of effective stowage so that it cannot, in the event of crash landing or ditching, injure passengers or crew by being flung around inside the fuselage. The problem then of the ability of aircrew and passengers to survive emergencies in the air and the ability to survive decelerations involved in crash landing and ditching of aircraft is largely that of design and therefore begins at a very early stage in the design of an aircraft. Any aircraft which is known to be difficult to abandon in flight or which has bad crash landing or ditching characteristics is not well received by the Services from the psychological point of view. Aircrew like to know that if in the event of an emergency they have to abandon the aircraft, there is a reasonable chance that they can do so satisfactorily and safely.

Survival at sea presents a problem and the ability of aircrew to survive under these conditions depends to a considerable extent on the ability of the designer to provide them with aircraft which will ditch and which can carry effective personal equipment and an effective dinghy and survival pack. All operational aircrew now carry a personal survival pack in the seat pan of the seat which they normally occupy and this pack accompanies them during emergency abandonment of the aircraft and contains a one-man dinghy, an exposure suit, radio beacon to assist in their rapid location, pyrotechnics, rations, water, a device for making fresh water from sea water, a hat, first aid outfit and other items to assist in survival, such as fishing gear, &c. This pack is attached to the life jacket in such a way that the parachute harness can be easily freed from the body after descent into water with the life jacket inflated. No permanent flotation can now be carried in a life jacket because of the space penalty. After descent into water the survival pack is released from the two side attachments to the life jacket and the remaining attached dinghy lanyard followed up until it terminates at the dinghy operating head. The pin is removed from this and it is turned to inflate the dinghy and then the airman climbs into his dinghy which he bales with the collapsible baler which is part of the dinghy equipment and removes from the pack the inflatable exposure suit into which he climbs after removing his flying boots. The inflatable exposure suit consists of two layers of rubber-proofed fabric stuck at regular intervals with an oral inflation tube which can blow the whole suit up in the space between these two layers. The effect is to provide a completely windproof coverage for the wetted airman and a considerable degree of insulation with the air between the two layers. The suit is extremely effective in insulation and protection but is difficult to put on without a considerable degree of practice, particularly in a one-man dinghy in a choppy sea. Location is of extreme importance and the life jacket will in future have fastened to it a radio beacon which can be picked up by search aircraft at a height of 15,000 feet from a radius of 75 miles. Investigation has shown that homing with this new radio beacon is extremely accurate and it should enormously assist in the location of downed aircrew. A secondary beacon, possibly with two-way speech, may be carried in the personal survival pack. Then it is necessary for aircrew to get themselves organized in their dinghies. Normally the captain of the aircraft is in charge regardless of rank, or the senior aircrew member if the captain is on a different dinghy or has been injured in the ditching. Dinghies are not now provided with paddles so it will be difficult for two aircrew who have descended by parachute in the sea to join forces. If this is possible it should be done as they will be able to economize in the use of their radio beacons, and their morale will be enormously raised by company. Water must be strictly rationed because water is the limiting factor in sea survival, together with cold. The exposure suit has with it a cushion which can be inflated and sat on, so that the seat is not directly in contact with very cold water if downed under Arctic conditions. A certain quantity of drinking water is carried in the water cushion on top of the survival equipment and under very cold conditions it may be necessary to keep this water cushion inside the exposure suit to prevent its freezing. The recommended procedure in the use of drinking water is to use no water for the first twenty-four hours and then to use between 10 and 14 oz. per day until one day's supply remains when the amount of water should be reduced to 2 oz. a day. Besides the water available in the water cushion water can be produced from sea water by the use of a chemical desalter or by the use of a sun still. Both methods produce more than the volume of the equipment of drinkable water from sea-water and under good conditions the sun still can provide adequate supply of drinking water indefinitely. The chemical apparatus is useless once the supply of desalinating chemical has been exhausted.

Every effort should be made to make the dinghy as conspicuous as possible to assist searching aircraft or launches. The use of sea-staining dyes materially assists in spotting from the air and the use of a very lightweight floating mat made of a neon-red fluorescent material will, it is hoped, increase the visibility of a dinghy considerably. Under hot conditions the exposure suit should not be abandoned completely but retained for use at night when the temperature is likely to fall considerably.

During daytime sweating should be limited by wetting clothing with sea water which will be evaporated by the small surface wind which is usually present, so that sweat need not be produced to obtain body cooling. Water must be strictly rationed and morale maintained by good leadership. The ability of an individual to survive depends on the amount of training he has had in the use of the equipment, on the amount of common sense he is blessed with, and on his desire to live.

Common dinghy ailments include motion sickness to which most motion sick individuals become accustomed after two days or so, and which can be treated by the tablets provided in the first aid kit. During this time they may get very severely debilitated. Salt-water boils occur after prolonged immersion of part of the body in salt water. They should be treated by light bandaging and should not be pricked or interfered with in any way. Sunburn must be protected against at all costs, and it is essential to keep the whole body covered with a light covering of clothing which may be wetted as desired, and to use an effective head covering and some form of protective eye-wear, such as goggles or a bandage or bandeau over the forehead to reduce the glare into the eyes.

Survival on land depends very largely on the type of country into which forced descent has been made. In the desert it is essential to remain with the aircraft which should be crash landed if at all possible. In this way the crew remain together, the aircraft is more easily seen from the air and offers some shelter from the extreme heat of the day. In addition the radio equipment may still be functioning and used to assist in location of the crash by the rescue organizations. Water must be strictly rationed and no attempt should be made to move from the scene of the crash even though the exact location is thought to be known unless other habitation of some sort can be seen for certain from the nearest high ground. All available use should be made of shelter, parachutes may be made into tents, double-thickness layers separated by two or three inches of air will provide good protection from direct sunlight, and use should be made of the shaded areas under the wing or tail of an aircraft, and, if possible, burrowing into the sand will produce a much cooler shelter than on the surface. A standing watch must be kept for searching aircraft and the recognized distress signal is three fires which may be made of any available inflammable material and parts of the aircraft—insulation, lagging, bits of rubber, oil drained from the engines, and the whole fire started with aircraft fuel. Black smoke can be produced by pouring aircraft engine oil on to a fire which has been well started by the use of aircraft fuel. The heliograph is extremely useful in attracting the attention of aircraft, as it is usually possible for a downed crew to see the searching aircraft very much sooner than the aircraft is likely to see them. As at sea, so in the desert, water is the limiting factor to the survival time of crews who have crashed there and they should be rationed in the same proportions.

Survival under jungle conditions is extremely arduous. Descent has, almost invariably, to be made by parachute, and individuals will therefore be on their own. There is extremely little chance of their joining up one with another, unless they are fortunate enough to land in a paddy field area. If it is at all possible the aircraft should be crashed landed. Generally, the terrain is such as to make this quite impracticable. In the jungle water is plentiful and the limiting factor will be the extremely slow rate of movement under very tiring conditions, the continuous pestilence of gnats, mosquitoes and flies, and probably a fear of the unknown and of the creepy-crawly animals and insects which are expected to be normal inhabitants of an extremely unpleasant area. After descent into jungle an attempt should be made to converge on to the site of the aircraft crash, because this will be far more conspicuous from the air than any other surrounding object. If the location of the crash is unknown, an attempt should be made to move downwards, down-stream, down river valleys, which generally lead towards civilization. A dinghy may be useful in descending rivers or fording rivers, and should not be jettisoned or destroyed if possible. The number of uses to which a parachute can be put are legion—it can be used for shelter, for making a hammock, or mosquito curtaining, as a filter for drinking water and for many other purposes. Food must be used sparingly and only training can teach aircrew how to use the food which they may find in the jungle itself. Many plants are poisonous, some animals and fish are poisonous and must be avoided. Footwear is of extreme importance and some form of jungle boot is essential if aircrew are to be able to move effectively. Aircrew must also have a good cutting implement.

Location is of extreme importance and a beacon must be operated from as high a ground as possible to obtain maximum range. Location with the new beacon should be so accurate that helicopter pick-up can be quickly effected, and if operational conditions permit additional survival equipment can be dropped to assist survivors.

Survival under cold conditions requires careful preparation and therefore begins before any flight over cold areas takes place. It is essential that all crews and passengers in aircraft should be properly equipped, and fitted with the appropriate type of clothing, which must be suitable first of all for use as flying clothing, to protect them against any emergency which may occur in the air and it must provide suitable protection in use under survival conditions in the country over which the flight is taking place. The clothing must be properly fitted and considerable attention must be paid to detail. Temperature is the limiting factor in cold weather survival: it is therefore essential that the aircraft should carry items of survival equipment designed to keep survivors warm by providing additional insulation, food, and means of producing water for drinking, additional items of hand and footwear,

but—most important of all—there should be a means of effecting rapid location. It is obvious that for all cold conditions it is almost essential to crash land the aircraft so that additional equipment which may be of use can be salvaged, in addition, of course, to the survival pack and dinghy. After the aircraft has been crash landed it should be abandoned rapidly and in an orderly fashion with all survival equipment items. Radio transmissions should be put out for as long as possible before a crash landing takes place so that the Rescue services have a reasonable chance of getting accurate fix over a greater range than can be effected by the various types of survival beacons and radio available in the aircraft.

Casualties should be removed from the immediate location of the aircraft and bleeding treated by compression bandages to restrict bleeding. Tourniquets should not be used as they predispose to frostbite. Casualties should be placed in a sleeping bag from the aircraft survival pack in shelter. The aircraft itself should not be used as shelter as even though it may be reasonably intact and windproof it will offer a very large area for the effusion of heat. The type of shelter will depend on the type of country. In barren land, snow caves, snow trenches or igloos can be made quite easily with a snow knife which should be in the aircraft pack, or with parts of the broken aircraft, or with a utility tool which it is intended to put into the survival pack. For the construction of igloos the right type of hard wind-compacted snow is essential. All forms of snow shelter are warm as snow is a good insulator, being ninety per cent air. Snow shelters can be made windproof by chinking all cracks with snow and the entrance to a snow shelter should be a tunnel underground below surface level away from the direction of the prevailing wind. Ventilation must be allowed to take place and a small hole in the roof and the entrance door should be sufficient, otherwise carbon monoxide poisoning may occur when gasoline-burning stoves are used for heating purposes. In bush country, shelter may be made from spruce trees fashioned into a lean-to shelter and thatched with spruce boughs, or a parateepee may be made or even a fully fledged log cabin. Tents are unlikely to be carried in aircraft but if provided must be of double-walled variety with very wind-resistant material and windproof closure and they must be simple to erect and stay put in high winds. The maintenance of body warmth is essential to guard against frostbite. Proper clothing must be provided and it must be used properly. The outer parka must have complete face protection and is an essential part of the aircraft survival kit. Hand and foot protection must be adequate and must not be tight or cause any constriction. Every effort must be made to avoid getting overheated and sweating into clothing as this reduces the insulation which is followed by chilling, freezing of sweat-wetted layers of clothing and ultimately death. The sleeping bag used must be simple, must be double quilted and of sufficient size. The face must never be put down inside a sleeping bag as the moisture from the lungs will then condense in it and wet it. The dishcloth scarf is used to control the neck opening of the clothing assembly and can be effectively used over the face as a mask when sleeping in the sleeping bag. Condensation occurs on the outside of it and freezes but there is sufficient insulation to keep the face from freezing in two layers of the scarf. All clothing must be kept dry and it is essential to dry hand and footwear, but not the outside mukluk, at least daily. Gloves and socks can be dried by body heat inside the sleeping bag, or may be dried over fires in bush country or where fuel is available or over the primus type stove when warming food or melting snow for drinking water.

The problem of cold weather survival is very largely protection from wind and cold. Wind is far more difficult to protect against than cold and it is essential that some form of shelter should be available even if it is only a trench dug in a snow bank. Wind rapidly removes the air from immediate contact with the body and promotes chilling.

The whole problem of survival on sea or on the ground in any part of the world depends on the efficiency of the very small quantity of equipment with which aircrew can be provided and upon the degree and efficiency of the training which they may be given in the art of survival. Training is of extreme importance for all phases of survival and wherever possible that training should be conducted under as severe a condition as possible.

The ability of aircrew to survive emergency in and to escape from their aircraft depends very largely upon the design of the aircraft itself. Consideration should be given to escape facilities very early in the design of any aircraft and wherever possible standard techniques should be adopted and standard equipment. Training of all aircrew personnel in the use of this personal survival equipment and in all survival techniques under the various conditions which may be encountered can do much to enable them to return to operational duty after an incident.

Squadron Leader D. G. V. Whittingham: *Survival and Rescue*

The medical aspects of survival and rescue which concern personnel of the Royal Air Force fall conventionally and easily into two parts. The first part embraces the many facets of the survival circumstance which occurs at high altitude. The second part concerns the survivor who has safely reached the ground or the sea and at first glance the ground survival condition presents problems completely different from the high altitude case. However logical and convenient it is to treat the problem of survival in two parts, in practice the division between the two is artificial for the sequence of events merge quickly and indistinguishably and equipment which has to serve the man for his emergency has always to be considered as a whole.

When considering equipment which will further a survivor's chances of rescue there is a rank order of importance which decides the arrangement of packs, character of training, and often the priority of research. It follows the needs of the survivor as they occur and applies both to high altitude and to ground survival but more particularly to the latter. It is to the ground survival case that we will refer in this instance, and the rank order of importance of necessary equipment to a survivor is as follows: (1) Protection; (2) Rapid location; (3) Water; (4) Food; (5) Ancillary aids. (The last group includes first-aid equipment: for general purposes major injury is in this instance excluded from the hazards of the complete survival emergency.)

Protection from the environment is understood in its broadest sense, to include not only equipment which the man may carry or wear, but also shelters which he may construct on the ground, and flotation devices for use at sea. There is continual improvement in the construction of apparatus to protect men from hostile environments. The development of boots for flying personnel which can be used for survival purposes provides an example of the way in which many of the applied and practical problems are dependent upon basic work.

During the 1939–45 war the majority of Royal Air Force flying personnel in Europe wore for flying a pair of boots designed to keep the feet warm but which were unsuitable for walking. These fleece-lined, suede, knee high, 1941 type boots are still in use. In 1943 a fleece-lined flying boot was introduced comprising a box calf shoe and a knee high and removable suede leg. The 1943 boot tended to make good those deficiencies of the 1941 type which made survivors conspicuous and uncomfortable during escape to friendly territory. It was realized that for a future generation of aircraft, boots for flying personnel would have to include features of design not existing in the 1941 and 1943 types. The problem of developing flying boots was further investigated and broken down into the following parts:

(1) General application of flying boots to future aircraft.
(2) Thermal insulation.
(3) Attachment of boots for marching and parachute descent.
(4) Design most inconspicuous and silent for escape and evasion.
(5) Materials (with reference to supplies in times of emergency).
(6) Traction and range of use of the footwear and increase in foot volumes during marching.
(7) The grading of the footwear.

It was discovered in survival exercises that for unpractised marchers lesions of the feet were the chief impediment to performance and that footwear which might be comfortable though closely fitted before the marching becomes almost unwearable as a result of foot swelling caused by the marching. An attempt was made to measure the increments of foot volume caused by marching, in two field exercises. In the first of these, six subjects walked approximately twenty-five miles a day for three consecutive days and foot volume measurements were taken before and after a day's march. In the second exercise this procedure was repeated for six unpractised marchers, but included six men accustomed to marching belonging to the Airborne Regiment.

It was found for the most part that foot swelling was the greatest impediment when associated with narrow footwear and encouraged the view that the best footwear for marchers is that which fits loosely. Although the sample included an increment of 10% on the initial foot volume, the range was wide, varying from 2% to 10% of the whole series of eighteen subjects, the mean being a 5% increment. The conversion of the volumetric increase to linear dimensions to enable the last maker to produce a last which would allow for possible foot swelling was not easy as the exact site of foot swelling could only be assumed to be mainly in the fore-part of the foot. At that time the precise histological location of the foot swelling was not an urgent requirement and various devices were used to further the main requirement, the production of a flying boot, without having to spend too much time on perhaps a more academic and fascinating part of the problem. Swelling was supposed to take place mainly in the fore-part of the foot and to that end loosely fitting footwear was designed. The size of the boot enables two pairs of socks to be worn and one of these can be removed if foot swelling is excessive. A special system of lacing was used to prevent any undesirable effects of the wide fore-part.

The second phase of the development comprised the sizing of footwear for flying personnel of the Royal Air Force. The development of a new size roll for footwear proved a considerable undertaking and from it has emerged the unique range of lasts which provides only two fittings in each size. In this way it is possible to equip the flying personnel population from a choice of sixteen possible sizes and fittings of boots, that is except for the extremes at each end of the range which are always in practice provided with bespoke footwear.

The survival of flying personnel, as described already, is dependent upon safe descent, protection against exposure to the hostile environment, rapid location and rescue, provision of sufficient water and sustenance. The limitations on bulk and weight on items for protection against exposure and the supply of water and food impose a demand for high efficiency on apparatus to aid rapid location and rescue.

It is well known that search by visual methods is both inefficient and time-consuming. It has been the practice of the past to use radio devices to aid air search but results until the past year had not shown any decisive improvements. Many aircraft are employed for what is virtually a visual search

pattern. Exposure to adverse extreme climatic conditions at sea and on land quickly reduces human efficiency and whilst primary protection must be provided and is of great importance, the most vital issue rests on a reduction of the time during which the man is exposed. This can only be achieved by quick and certain rescue. It is true that the rapid location of the survivor is of prime importance physiologically, and much attention has been paid to a recent advance in survivor location which at one bound could well reduce many of the survival and medical problems associated with exposure, lack of water and food.

A system has been developed which appears to overcome the important defects in the present air search and location methods. The equipment consists of a small transmitter attached to the person which when switched on emits a powerful pulse of high-frequency energy, the unipolar aerial being erected at the same moment by the action of switching on.

The transmitter is held on the anterior flotation chamber of the inflated life-saving waistcoat from which position it is easy to strip the rubber cover to the aerial and switch on the instrument. A receiver carried by the rescue aircraft can recognize the signal a relatively great distance away, and can home very accurately when a null indicates that the rescue aircraft is immediately above the survivor. The important function which this equipment offers is that the receiver can be fitted to boats and rescue launches which can recognize the signal and home to visual contact by day or night. It is thus expected that search times will be limited only by the speed of the means of surface rescue. Aircraft may be used to locate the position of "ditched" personnel and radio this information to rescue launches or amphibious aircraft.

Of course, there are many facets of this which cannot be described here. A device of this sort implies a new receiver fitted to multi-seater aircraft, it implies a special means of talk-back between survivor and rescue aircraft and the standardization of this method between those nations which may be using a common rescue system. These are problems which are being resolved gradually. Most important at the present moment is the availability to the Royal Air Force of a device to enable effective rescues to be made in the very near future in any conditions. The device can be used in helicopter rescue and it is hoped that rapid recovery of survivors will be commonplace in times of emergency.

Royal Air Force experimental rations have been made up to meet the dietetic requirements of a survivor in whatever environment he may find himself. In temperate climates where a survivor might have to walk several hundred miles before being rescued it is possible to include quite a high proportion of fat in his ration since he is most likely to be able to find a good supply of drinking water. This also applies to many areas of the jungle and the tropics. For desert survival there is no alternative to supplying the man with a survival pack, the greater part of which is water. In the cold weather regions of the Poles the inclusion of fat in the ration is indicated, provided it is within physiological limits, since the man must have a means of providing himself with shelter to live, and if he has this he should be able to provide himself with water. Sea survival in any of the above climates is influenced particularly by the physiological effects of heat and cold and water balance, as well as a possible shortage of food. The supply of water can be satisfactory, but not plentiful, for fairly long periods by using desalters or a solar still, or collecting rain. In this case a high fat ration is not indicated. If the complete ration were in two parts, one rich in carbohydrate and the other rich in fat, in such circumstances where the survivor finds he is short of water he could reject the fat rich part of the ration, which would be appropriately labelled. This rejection may be especially necessary during sea survival. The Royal Air Force packs have been made in two parts to meet these varying conditions of survival:

The Universal Component in which the carbohydrate fraction is high and of the order of protein/fat/carbohydrate as 1 : 2·8 : 7·8.

The Land Mass Supplement which contains pemmican, butter and biscuits. When used in conjunction with the universal component the proportion of protein/fat/carbohydrate is changed to 1 : 2·5 : 5·2. The combined ration is intended for extreme cold weather, cold temperate and land mass survival, excluding desert.

The universal component weighs 3 lb. gross, has a volume of 80 cu. in. and dimensions 10 in. × 4 in. × 2 in. It supplies 4,771 calories approximately.

The land mass supplement weighs 1½ lb. gross, has a volume of 40 cu. in. and dimensions 5 in. × 4 in. × 2 in. It supplies 2,034 calories approximately.

The combined ration weighs 4½ lb. gross, has a volume of 120 cu. in. and dimensions 15 in. × 4 in. × 2 in. It supplies 6,805 calories approximately.

It is considered that the combined ration if used efficiently will maintain a man, doing very hard work, for three days. Water must be found and purified by chloramine or by boiling.

One complete pack, if necessary, will maintain a man up to a maximum of seven days or longer if he is not engaged in strenuous work.

It is possible for a fit man to march 30 miles a day for three days or more eating only the contents of a combined pack, in a temperate environment, providing he finds 2½ pints of water each day.

All the foodstuffs in the pack can be eaten cold, except the tea/milk/sugar powder, and can be warmed near the body to improve their edibility in very cold weather regions. Being made of traditional foodstuffs and having familiar tastes it is unlikely the components will be rejected for lack of acceptability.

A high fat diet in circumstances of water lack is undesirable when hard work is being carried out because of its ketonic effect, its subsequent heavy solute load on the kidney and increase in water requirement. On the other hand, the inclusion of protein and fat increases the acceptability of a ration, which is of importance during the first three days of survival when, it has been found for the most part, appetites are poor despite the expenditure of much energy.

The place at which to draw the line has been decided in the main during the course of five major field exercises where various groups of men were provided with rations differing in their proximate constituent ratios. The men themselves kept a record of the food they ate and their accuracy was checked by examination of the components they returned and by cross reference to diaries of day-to-day activities. Much depends on the nature of the food eaten and the simplicity with which it can be described in food questionnaires. The food components under review were in units which could be completely eaten or broken down into portions which made accurate weighing in the field unnecessary. From the field work two points were once again confirmed: the first, that a man, however exhausted, will prefer to go to the trouble of living off the land if his ration is unacceptable, and secondly that walking at least 28 miles a day in winter temperate environment can be achieved when consuming very low calorie intakes of the order of 575 calories. (The range of this for three men was from 215 to 1,306 calories over seven days.)

Much insight into the problem of survival feeding is gained from practical experience under simulated survival. The trials are associated with some physical discomfort and work in the field has proved expedient and useful for the appraisal of factors other than the immediate one at hand.

More especially does it show that in survival as a whole many unexpected circumstances can often vitiate the best physiological intentions of designers of survival equipment.

By describing the broad outlines of three recent changes in survival equipment it has been hoped to show the diversity of the medical interest. In the development of personal equipment for survivors the co-operation of a small development group comprising representatives of those specialties which play a major part in the ultimate production of an item is beneficial. The flexibility and compact nature of such a group can often save prolonged and expensive investigations provided it has good experimental facilities to draw upon.

Squadron Leader T. N. N. Brennan: *The Jungle Survival Pack*

(1) During a recent tour of duty as Deputy Principal Medical Officer (Flying) of the Far East Air Force (R.A.F.), the problem of designing a jungle-survival pack to supersede the pack which had been in use for many years was given attention. Criticism of the pack in use included complaints concerning the moisture condensation inside the rubberized-fabric container, with resulting corrosion of metal items and deliquescence of salt and fire-making tablets. The official method of fixture of the pack to the Mae West (flotation waistcoat) also gave rise to complaints of discomfort, especially in the smaller cockpits of the more modern fighter and fighter-bomber aircraft which are now being used.

(2) A new pack was designed as a seat-type pack instead of a back-type pack, thereby economizing valuable cockpit space. The contents of the prototype pack included many innovations, some of which were borrowed from a prototype back-type jungle-survival pack which had been designed at the Royal Air Force Institute of Aviation Medicine, Farnborough. This pack, while containing many worth while improvements, was considered by testing aircrew to be unsatisfactory by reason of in-flight discomfort.

(3) Innovations contained in the F.E.A.F. prototype pack included an improved Bowie-type jungle knife, a hard-wearing rubberized fabric water bottle, a sun hat with a malleable wire brim, from which could be suspended the tubular mosquito-proof veil, and, later, items of a greatly improved food component were received. Added locally was a small flat version of the Army Tommy Cooker, a cooking stove which carried its own solid fuel inside when not in use. The F.E.A.F. type carried thirty fire-making tablets, and was about the size of two packets of twenty cigarettes.

(4) An exercise to give a thorough trial to this new pack was organized, and, as the prevailing state of guerilla warfare existed in Malaya, it was decided to stage the service trials in Sarawak, which contained jungle, swamp, and other terrain very similar to that experienced in Malaya.

(5) In the arranging of the actual route to be followed, and in choosing the trials team, one other factor was kept in mind. This was the morale-building aspect of a successful, though necessarily arduous, trek through difficult country by members of aircrew, who had heard of few escapes from crash landings in jungle terrain in Malaya, and who, therefore, had a rather fatalistic attitude about the possibilities of travel, survival and rescue in such surroundings.

(6) Five members of F.E.A.F. squadron aircrew, one member of the F.E.A.F. Jungle Rescue Team, based at Singapore, and myself as Officer in Medical Charge, and Medical observer made up the trials team. Clothing was as worn by aircrew operating in Malaya, which included a khaki lightweight flying overall, jungle boots (Army pattern), and sun hat and gloves from the survival pack. Pistols were carried, and in addition I carried a small haversack containing extra medicaments and anti-venin. Each member also carried a half parachute, which for the purpose of the exercise was presumed to have been used to escape from an aircraft. The full parachute, especially if damp, is

too heavy to carry. The parachute nylon was used as bedding, for signalling to aircraft, straining water, bandaging, and would have been utilized for makeshift clothing and footwear if necessary.

(7) The team landed from a shallow draught canoe many miles up a tributary of the Sungei Sadong in First Division of Sarawak, and travelled in swamp jungle for the greater part of the first four days, with some treking through scrub, and one day across a valley through thick elephant grass in a few feet of swamp water. On the fifth day a 2,500 foot hill was crossed, and a ten mile march brought us down to a village on a river. During the next two days we travelled down river, sometimes in canoes, often on foot through jungle across wide bends of the river, and at last reached a small town at the estuary, from which we were picked up by motor boat and taken back to Kuching.

(8) The exercise was a great success. All members of the team stated that, in retrospect, it had been well worth while, though there were many times during the march when morale had been on the ebb.

(9) Aspects of medical interest in the results of the trial:

(*a*) *The effective temperature* in jungle is high, as the relative humidity is always high, and the air movement minimal. Temperatures experienced varied between 78° F. in the morning and about 90° F. at midday, and relative humidities between 94% and 80%. With this R.H. sweat loss is in the region of 5–6 litres/day. Water was to be had in abundance, and this swamp water, strained and purified, caused no ill-effects. Salt was taken from the start by all except two of the party. These two members both showed symptoms of salt lack on the second and third days, one suffering an acute heat exhaustion, from which he recovered swiftly on ingestion of 1·0 gramme salt with a pint of water. The amount of salt taken per day by the members was from 10 grammes up to 15 grammes. This is considerably below the salt requirements for the tropics for a man doing hard physical work as tabled by various experienced physiologists. The decision to limit salt ingestion to this degree was made for the following reasons. (i) Each member started out with a constitution conditioned to the tropics, i.e. more than a year in Malaya or Singapore. (ii) Each member had a plasma chloride within the limits of normality. It is of interest to record here that the two members who did not take salt at first, and showed symptoms of lack both had plasma chlorides in low limits of normality. (iii) The ingestion of a recommended 29 grammes of salt/day, or nearly sixty 0·5 gramme tablets would have probably affected digestion of the small amounts of food on which we had to subsist, and might have caused sickness. As it was, there were no ill-effects. This exercise also bore out the observation that the introduction of strong incentive and good morale do not alter the critical level of effective temperature at which deterioration of effort takes place.

(*b*) *Malariology*.—Preventive measures carried out included the ingestion of two tablets of Paludrine (0·2 gramme) on the day before entering the jungle, and one tablet per day thereafter, wearing face-veil and gloves at night, and application of Sketofax to face and hands. All members suffered from biting insects at night, many of which must have been mosquitoes, though there were many sand-fly type observed. All mosquitoes seen were anopheline. McArthur, in his pamphlet "History of Malaria in Borneo" incriminates the solitary jungle-breeding *A. leucosphyrus* as the vector of malaria in Borneo. No member of the trials team caught malaria.

(*c*) *Ankylostomiasis*.—One member of the team complained of an eruption and blistering in three places on his legs some five days after return to Singapore from Kuching, and on examination showed a classical larva migrans invasion at two places on one leg and at one place on the other leg. Freezing and local treatment resulted in complete healing, with no further complications. Repeated stool examinations during the succeeding six months excluded other ankylostome or schistosome infection. The *Ankylostoma brasiliense* from which this member suffered was acquired from contact with a dog at one of the villages at which a night stop was made.

(*d*) *Leeches*.—During the climb over the hill on the fifth day, many leeches were seen, and all members were affected. De-leeching was carried out at routine halts, generally with the aid of a cigarette end. Cigarettes were carried in a waterproof container as an item in the pack.

(*e*) *First-aid component*.—It was recommended that a suitable antiseptic should be carried in future. Cetavlon jelly was carried in this instance, and proved satisfactory. The inclusion of sulphaguanidine instead of a cathartic was also recommended. The minimal amount of food ingested during a survival march should render the inclusion of a cathartic of little use, whereas the ever-present possibility of dysentery, whether infective or non-specific, must be guarded against.

(*f*) *Other requirements*.—Talcum powder, to dry and recondition the feet after a day march, whether the moisture is sweat or swamp. A small cake of soap is also considered a requirement, though wood-ash with water can be utilized for washing. Toilet paper, taking up little space in the pack is thought to be worth inclusion.

(10) An important possession of all members of aircrew is the knowledge of the best way to use their survival equipment, and a knowledge of the terrain over which they fly, whether it be jungle or desert or Arctic. For aircrew flying over the jungle this means indoctrination in recognition of plant life which can be used to advantage for sustenance, whether for eating, for drinking, or for building a shelter. The means of trapping or catching animals or fish is also important, as the actual edible fruits and plant life in the jungle are few, and not easily found.

Section of Experimental Medicine and Therapeutics

President—Professor R. V. CHRISTIE, M.Sc.McGill, D.Sc.Lond., M.D., F.R.C.P.

[*December* 9, 1952]

Erythromycin [*Abstract*]

By M. J. ROMANSKY, M.D., F.A.C.P.

George Washington University School of Medicine, Washington, D.C.

THE reaction of organism and patient to an antibiotic determines its clinical use. The increasing resistance to penicillin of certain organisms should lead to a more discriminating use of the drug. The superimposition of a resistant strain of staphylococci may produce a state of affairs very difficult to control, and, so far, once resistance to an antibiotic has appeared we have not yet found any agent to reverse it. The increasing resistance of certain organisms to penicillin makes it necessary to use new or other antibiotics. Nevertheless, organisms such as the pneumococcus, Group A beta streptococcus, the meningococcus and the gonococcus as yet have given no signs of developing resistance to penicillin.

The development of resistance to streptomycin can occur with extreme rapidity. Even to the broad spectrum antibiotics there has been a progressive increase in resistance.

Resistance to aureomycin can mean resistance to terramycin even if the organisms have not been treated by the latter, and if there is no resistance to aureomycin it is reasonable to expect no resistance to terramycin.

Two other factors are also of importance, namely the effect of cortisone on the resistance of the patient to infection leading to difficulties in controlling such infections with antibiotics, and the problem of the blood dyscrasias. Since 1937 there has been a tendency to progressive increase in the blood dyscrasias, i.e. from the time of the introduction of the sulphonamides onwards. Part of this trouble is due to lack of discrimination in the use of antibiotics and the newer drugs.

The newest antibiotic erythromycin given orally, offers a fairly simple method of producing a high level concentration in the blood. It is not active against Gram-negative organisms except the diplococci, but it is very active against the Gram-positive group, whether sensitive or resistant to the other antibiotics, and particularly the staphylococcus. It is inactive clinically against the tubercle bacillus. Despite its degree of restricted action it promises well.

Some of the troubles of the broad spectrum antibiotics may be because their effects on the intestinal flora are too wide ranging. The type of infection and sensitivity of the organism must, in the future, determine the degree of specificity of the antibiotic required.

[*February* 10, 1953]

DISCUSSION: THE ASSESSMENT OF RESPIRATORY FUNCTION

Dr. C. B. McKerrow, Pneumoconiosis Research Unit, Llandough Hospital, Cardiff.

Assessment of the Mechanical Function in Ventilation

Study of the mechanics of breathing in man may be approached in two ways: In the first place the function as a whole may be estimated by tests such as the maximum breathing capacity. Here we are asking the subject to apply his maximum effort in breathing, and we measure the output obtained. These tests are simple to do and, on the whole, show good relation to disability. But they have two obvious disadvantages: firstly, they require complete co-operation of the subject, and, secondly, they measure merely the overall function, and make no attempt to analyse the cause of any deficiency found.

In the second method of approach, we attempt to analyse the mechanics of respiration in physical terms. For instance, we estimate the bronchial resistance, or the elastic and viscous forces of breathing. We shall consider these two groups of tests separately.

I.—Tests of the Overall Function

The three tests most commonly used are the vital capacity, the maximum breathing capacity, and the measurement of mean flow rate of a single maximal expiration.

It is helpful to consider them in relation to the following criteria:

(*a*) Sensitivity: i.e. what is their accuracy relative to what is being measured? This is dependent both on instrumental accuracy and on the range of values between clinically normal and abnormal subjects.

(*b*) Validity: i.e. does the test measure the right thing or is the result influenced by factors not intended?

(*c*) Simplicity: Is the test a practical one, both from the point of view of apparatus needed and from the demands made on the subject?

(1) *Vital capacity.*—The vital capacity has two disadvantages as a test: firstly, the range of values in normal and abnormal subjects overlaps to a large extent; thus its sensitivity is poor. Secondly, it is essentially a static measurement and is therefore scarcely a valid test of mechanical function. It is measuring the stroke of the respiratory pump regardless of its rate. Thus patients with severe respiratory disability often have surprisingly large vital capacities, although it is clear from the slow forced expiration with which they perform the test that much of the expired volume can be of little use to them when having to hyperventilate on exertion. The chief advantage of the test is its simplicity both in performance and in the apparatus needed.

(2) *Maximum breathing capacity.*—In this test, the subject is asked to put his maximum effort into breathing for about 15 seconds, and the volume of air he has moved is measured and expressed as litres per minute.

The test is measuring flow per unit time and is therefore a dynamic measurement, although it is assessing the mechanical function of the lungs in a somewhat artificial way.

The test is fairly simple to do, and the range of values between normal and abnormal subjects is very wide. But it has the important disadvantage that results are surprisingly variable in the hands of different workers. Average values for normal subjects reported in the literature range from under 100 litres/minute to nearly 200 litres/minute. Some of this discrepancy is due to differences in technique in performing the test, and to differences in ideas on what constitutes a normal subject. However, much of this variation seems to be due to two causes related to the instrument used.

(i) The instrument may measure inaccurately in certain circumstances.

(ii) It may modify the subject's response by presenting a high resistance to airflow, or by influencing his rate of breathing.

It is worth considering these factors in instruments commonly used for measuring the M.B.C. as the test loses much of its value if the results obtained apply only to one particular instrument.

The Benedict-Roth spirometer has been used by many workers for estimating the M.B.C. and the serious error which may occur during hyperventilation was first recognized by D'Silva and Mendel (1950). They found an error of up to 40% in their particular spirometer due to an oscillatory movement of the water within the bell.

The use of a Tissot's spirometer for collection of expired air during hyperventilation is also not free from error. In a common system of this type, the subject inspires through a valve from a bag containing a 5% CO_2 mixture and expires through a second valve into the spirometer, which thus moves during expiration but should come to rest during inspiration. However, in hyperventilation the bell may fail to stop immediately at the end of an expiration, and be carried on by its momentum, thus drawing air from the inspirate bag. The lower the resistance of the valves and the less the friction in the spirometer, the larger is the likely error. In a 100 litre spirometer of this type, we found a positive error of over 10%.

Recently we investigated the effect of airflow resistance on the M.B.C., and were able to obtain an estimate of the likely fall in M.B.C. values with increasing airflow resistance. These results emphasized the necessity for using mouthpieces, tubing and valves of considerably lower resistance than those commonly employed, but also showed that it is practicable to design a machine with resistance low enough not to affect the results.

The choice of apparatus for measuring the M.B.C. must be influenced by the number of subjects to be tested, the likelihood of transmission of infection and also expense.

One of the simplest but least portable methods is the use of two Douglas bags, a three-way tap and a low resistance valve box. The expired air collected during an exact fifteen-second period is collected in the Douglas bag for subsequent measurement by a gas meter. The Douglas bags must have much larger tubes (minimum bore of 1½ in.) than are usually fitted, and the tap should have a bore of at least 1¼ in.

A spirometer may be used provided that the inertia and resistance to airflow is low. Bernstein, D'Silva and Mendel (1952) have recently described an improved recording spirometer, which is free from the error due to water oscillation, but they provide no figures for the resistance to airflow.

When large numbers of subjects are to be examined, it is an advantage to obtain direct readings without the necessity of analysing spirometer tracings, and we have therefore developed a simple apparatus employing a dry gas meter. The instrument has a low resistance to airflow, is virtually free from inertia, and has been constructed so that the part through which the subject breathes can be changed complete after each test to eliminate the risk of transmission of infection. The apparatus is shown in outline in Fig. 1.

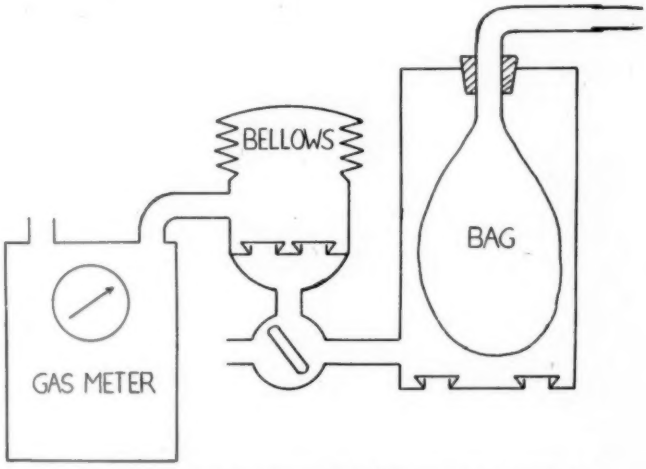


FIG. 1.—Diagram of the gas meter M.B.C. apparatus (*see* text).

The subject breathes in and out from the 7-litre closed rubber bag contained within a metal tank. As he inspires, air is drawn into the tank through the inspiratory valves[1] in its floor. As he breathes out, the clean dry air is displaced from the tank through a three-way tap leading to the expiratory valves and thence to a chamber, the top of which consists of rubber bellows from a Sanborn metabolism apparatus. During the fast part of an expiration, some of the air inflates the bellows while the rest passes on through the 400 cu. ft./hr. gas meter[2] (Fig. 1). During the subject's next inspiration, the bellows have time to deflate by their own weight driving their contained air through the gas meter, so that essentially the discontinuous airflow of expiration has been transformed into a continuous flow through the gas meter at a proportionately reduced flow rate. This arrangement not only gets over the effects of the inertia of the gas meter, but greatly reduces the airflow resistance. In fact, the peak airflow resistance encountered in this apparatus is considerably less than in most spirometers (peak 2·2 cm. H_2O at M.B.C. of 135 litres/min.).

After the test, the bag, tube and mouthpiece detach complete for cleaning and are replaced by a fresh set. The air in the rest of the apparatus is, of course, always clean. The gas meter itself is

[1]Low resistance valves (which should be used in pairs in M.B.C. apparatus) may be obtained from Warren E. Collins Inc., 555, Huntington Avenue, Boston, Massachusetts.

[2]Messrs. Parkinson & Cowan (Gas Meters) Ltd., Cottage Lane, City Road, London, E.C.1, manufacture a 400 cu. ft./hr. meter, which they have slightly modified to make it suitable for M.B.C. measurements.

suitable for measuring the exercise ventilation in the Hugh-Jones step test (Hugh-Jones and Lambert, 1952).

(3) *Measurement of the expiratory flow rate on a single expiration.*—Tiffenau *et al.* (1949) in France, Kennedy (1953) in this country, Kadlec and Vyskocil (1950) in Czechoslovakia, and Gaensler (1951) in the U.S.A. have measured the volume expired in a short time following a full inspiration. Kennedy, after an analysis of these expiratory spirograms, came to the conclusion that the volume expired in 0·75 second with full effort correlates highly with the M.B.C. We recently compared the M.B.C. with these timed expiratory volumes on a mining population and obtained a correlation coefficient of 0·8 between them. It is too early to say whether this test will correlate as highly as this in other respiratory diseases, but there is no doubt that it requires less co-operation on the part of the subject than does the M.B.C. test, is less tiring, and is thus particularly suitable for field work and for patients who are severely disabled. The subject is simply required to take a full inspiration and then exhale as fast as possible into the spirometer. We normally take the mean of three attempts. The repeatability of the test is very good and the standard error of the mean of three readings is only 2·7%. It certainly appears worthy of further examination, and in our opinion may well supplant the M.B.C. as a simple routine clinical investigation.

The apparatus needed is either a fast recording spirometer, as used by Kennedy (1953) or, if a large number of subjects are to be tested, the electronically timed apparatus described by Gaensler (1951) may be an advantage. We are using this automatic apparatus ourselves, in a somewhat modified form.

II.—Analysis of the Mechanics of Breathing

We come now to the test procedures which aim at testing the components of mechanical function. They attempt not merely to show whether the respiratory mechanics are faulty, but also to indicate the physical cause of the impairment.

Table I shows in a simplified form the essential aspects of respiratory mechanics. It is perhaps

Table I.—The Essential Features of Respiratory Mechanics

Inspiration	Expiration
Force assisting inspiration:	*Force assisting expiration*:
Muscular component:	Muscular component:
Chest wall. Diaphragm.	Usually absent.
Elastic component:	Elastic component:
Chest wall elasticity.	Lung elasticity.
Force opposing inspiration:	*Force opposing expiration*:
Elastic component:	Elastic component:
Lung elasticity.	Chest wall elasticity.
Viscous component:	Viscous component:
Tissue resistance. Air resistance.	Tissue resistance. Air resistance.

helpful to look on the respiratory movements as being simply the expression of temporary imbalance between two sets of opposing forces. Thus, on inspiration we have the muscular force of the intercostals and diaphragm, and the elastic recoil of the chest tending to increase its volume, opposed by the elastic and viscous forces within the lungs and chest wall.

In the case of the elastic force, the magnitude is related to the depth of the inspiration, whereas the viscous force is related to the speed of movement and hence to the airflow rate. The elasticity of the lungs is usually measured as "elastance" (Bayliss and Robertson, 1939) or pressure required to produce unit change in volume. The viscous forces arise from two sources. Firstly, the viscous resistance of the tissues of lungs and thorax to deformation, and secondly the viscosity of the airflow through the airways. Viscous resistance is generally measured as "viscance" or pressure per unit flow of respired gas. Perhaps a crude, and I am afraid, imperfect analogy may help here. Suppose we were blowing up a balloon, the resistance we encountered would be due partly to the amount the rubber was stretched, and partly to the difficulty we had in forcing air through the narrow neck. The former resistance would depend on the volume of the balloon—elastance—and the latter on the speed we were blowing, the air viscance. It should be mentioned that this usage of the term "air viscance" is not strictly in accordance with Fenn's terminology. He and his colleagues would use "air viscance" to denote only the streamline component of air resistance, and use the term "turbulent resistance" to denote that part of air resistance due to air turbulence. On expiration, the force is provided by the elastic recoil of the lungs (except during maximal expiration when it is assisted by the abdominal muscles), and is opposed chiefly by air and tissue viscous resistance in the same way as in inspiration.

It will be apparent that alteration in any of these components of the mechanism will alter the performance of the respiratory pump, and various attempts have been made to measure the individual components.

The total force available for respiration has been investigated by Fenn (1951) and his colleagues, and is expressed in their pressure-volume diagram of the chest. These data have been obtained by

measuring the maximum inspiratory or expiratory pressures attainable when sucking or blowing against a mercury manometer at different respiratory levels.

The air viscance has been estimated by Otis and his colleagues by measuring the alveolar pressure necessary to produce a given airflow. The method used is one originally proposed by Von Neergaard and Wirz in 1927, and depends on the fact that if the flow of air from the lungs is momentarily interrupted, the pressure gradient in the airways disappears, and the pressure recorded at the mouth is equal to that in the alveoli.

Measurement of tissue viscance has been attempted by Otis, Fenn and Rahn (1950) on subjects relaxing in a Drinker's respirator. Here the work of breathing is done by the respirator and, knowing the air viscance determined by the interruption method, it is possible to calculate the tissue viscance.

Recently Dornhorst and Leathart (1952) published a method of measuring both elastance and viscance of the lungs alone from œsophageal pressure tracings and pneumograph records. The method depends on the fact that œsophageal pressure closely follows the intrapleural pressure, and is therefore an index of the forces operating on the lungs. The phase relationship between the pressure record and the pneumograph indicates the type of resistance. Thus, pressure recorded at the end of an inspiration or expiration is due to elastance only as there is no airflow, and that recorded during respiratory movement is due both to elastic and viscous components.

All these procedures with the exception of measurement of the total force available for respiration require relatively complex apparatus, and are considerably more time consuming than such simple tests as the M.B.C. It cannot be claimed that they yet represent more than an early attempt in the analysis of the mechanics of breathing. There is much to learn about them before we can assess their clinical value, but it seems likely that the more general application of this type of test may result in a great extension to our knowledge of the mechanical factors in respiratory disability.

REFERENCES

Bayliss, L. E., and Robertson, G. W. (1939) *Quart. J. exp. Physiol.*, **29**, 27.
Bernstein, L., D'Silva, J. L., and Mendel, D. (1952) *Thorax*, **7**, 255.
Dornhorst, A. C., and Leathart, G. L. (1952) *Lancet*, ii, 109.
D'Silva, J. L., and Mendel, D. (1950) *Thorax*, **5**, 325.
Fenn, W. O. (1951) *Amer. J. Med.*, **10**, 77.
Gaensler, E. A. (1951) *Science*, **114**, 444.
Hugh-Jones, P., and Lambert, A. V. (1952) *Brit. med. J.*, i, 65.
Kadlec, K., and Vyskocil, J. (1950) *Pracovni Lekarstvi*, **6**, 348.
Kennedy, M. C. S. (1953) *Thorax*, **8**, 73.
Otis, A. B., Fenn, W. O., and Rahn, H. (1950) *J. appl. Physiol.*, **2**, 592.
Tiffeneau, R., Bousser, J., and Drutel, P. (1949) *Paris méd.*, **39**, 543.
Von Neergaard, K., and Wirz, K. (1927) *Z. klin. Med.*, **105**, 52.

Dr. D. V. Bates, St. Bartholomew's Hospital: Dr. McKerrow has described how the bellows action of the lungs may be measured, and when this has been done there are at least two further aspects of lung function on which we require information. The first is "how evenly is the gas distributed within the lungs?" and the second "how efficiently is the blood ventilated?"

In the last decade a great deal of light has been shed on the evenness of inspired gas distribution within the lungs. This aspect of lung function is conveniently studied by the use of helium or nitrogen as indicator gases and three main techniques have been used. The first consists of the analysis of gas composition of a single breath; the second in analysing the rate at which equilibrium is reached in a closed circuit; and the third is by measuring the rate of gas replacement in the lungs using an open circuit system. Each of these methods has merits not possessed by either of the other two, but the overall results do not appear to be greatly affected by the choice of technique except in particular circumstances. This work has led to four conclusions of importance:

(1) That normal people have some degree of uneven distribution of inspired gas within the lungs.

(2) That this becomes progressively more uneven as one gets older in the absence of any respiratory disease.

(3) That the evenness of gas distribution is upset by anything that interferes with the almost even expansion of lung. Thus it becomes uneven in a wide variety of conditions, asthma, emphysema, chest deformity, cystic lung disease, &c.

(4) That there may be markedly abnormal gas distribution in patients with asthma who are symptom free and without clinical evidence of bronchospasm at the time of study.

Further work in this field may clarify the mechanisms underlying these changes and perhaps enable us to understand the changes of function in terms of pathology.

Having found in a certain patient that inspired gas is unevenly distributed, we now require to know how well the blood is ventilated. It is evident that a minor degree of uneven distribution of gas may make very little difference to overall lung function, particularly if blood perfusion has been adjusted so that very little blood is passing through poorly ventilated lung. Accordingly we need to know how well perfusion is balanced to ventilation, and whether the rate of gas transfer across the membrane of the alveoli is normal. I propose to omit discussion of measurements that throw light on the overall

picture of blood ventilation, such as the actual oxygen saturation or arterial CO_2 tension, since these do not help us to understand the nature of the process that is responsible for the abnormality. As far as lung function as a whole is concerned we can have a number of different gas-blood relationships within the lung. There may be:

(1) Almost even gas distribution and even blood perfusion as in health.

(2) Even gas distribution but uneven blood perfusion or "shunting" of blood: an arterio-venous fistula in the lung is an extreme example of this.

(3) Uneven gas distribution but blood distribution still even throughout the lung; this possibly occurs immediately after a spontaneous pneumothorax.

(4) Uneven gas distribution, but blood distribution balanced to it. In this condition, well ventilated parts of the lung have a good perfusion and poorly ventilated parts have a reduced perfusion. Asthma uncomplicated by emphysema and congenital cystic disease of the lung may provide examples of this.

(5) Uneven gas distribution and uneven blood distribution not balanced to ventilation. This state of affairs almost certainly arises in emphysema.

But in addition to these relationships, the physical characteristics of the lung membrane may be varying in the lung, and this change may accompany any of the patterns just described.

I think you will agree that the detailed quantitative unravelling of the problem of what is happening in a particular patient will inevitably be complex. Dr. Riley (Riley *et al.*, 1951), in a major contribution to this field, has considered in detail what may be learnt from the simultaneous analysis of gas exchange and of gas tension within the blood. From these figures a calculation may be made of the overall pressure gradient of O_2 within the lungs. Further, by ingenious use of the peculiar shape of the Hb dissociation curve, he has been able to separate, at least approximately, the effect of impaired diffusion on the one hand, and of blood perfusion of non-ventilated lung on the other. The method of expression of results in this technique, and the validity of some of the assumptions that have to be made in it have both recently been questioned, and it is clear that considerable caution must be exercised at this stage in equating apparent change of diffusion capacity in different conditions with patterns of pathological change within the lung.

The problem of efficiency of "blood ventilation" has recently been attacked by the use of carbon monoxide. To my knowledge this technique has been used at the Pneumoconiosis Research Unit and at St. Bartholomew's Hospital in this country, and at Dr. G. W. Wright's Department at Saranac Lake and at the Graduate School of Medicine in Philadelphia in the United States. The results I shall quote here have been obtained in one or other of these centres and they are not to be taken as consisting solely of the work at any one of them.

What is the purpose of using CO? In simple terms its peculiar property of rapid combination with hæmoglobin means that the rate of disappearance of the gas from an alveolus is determined principally by the ease with which it can traverse the alveolar membrane. Further, the rate of disappearance is not initially much affected by how much has already entered the blood, and so in general terms and in particular conditions it will exert no "back pressure".

The rate of uptake of CO is measured in a simple open circuit continuous breathing experiment. Infra-red gas analysis methods have greatly simplified the work involved. Using this method, it was soon found that the percentage removal of CO from the inspired gas was much reduced in emphysema, but that asthma without emphysema did not produce a similar fall. Those using the CO technique have found that it appears to be a sensitive index of the severity of emphysema and to be, therefore, of considerable prognostic value.

What is it measuring? Recent work at the Graduate School of Medicine in Philadelphia has clarified some of the theoretical aspects of carbon monoxide uptake. It has been shown that the percentage CO uptake is dependent on the balance between ventilation and diffusing capacity within the lung, and the finding of a lowered percentage uptake of CO tells us that the "blood gas interchange" in the well ventilated parts of the lung is not normal. This is the case in emphysema. We do not know whether this is due to actual change in the alveolar membrane or to a reduction in area of the pulmonary vascular bed. In asthma it seems that the lung is able to maintain a normal or better than normal diffusion in areas of the lung that are being well ventilated. In cases of thoracic deformity, many aspects of lung function may be found abnormal—the vital capacity is much reduced, the maximal breathing capacity is low, and the gas distribution may be uneven throughout the lung. There is evidence to suggest that in these people the CO uptake is normal in the presence of these abnormalities until cor pulmonale begins to develop, when it starts to fall significantly.

I would like to end by illustrating the use of function tests in following the course of patients with emphysema. Fig. 1 illustrates the change in function tests in a case of moderately severe emphysema in a man of 61 years of age. Over four years there has been very little change in performance in these tests. Clinically, too, he has not altered very much in this period.

FIG. 2 shows changes in the same tests in a younger patient. In this man, now aged 35, over the same period there has been a steady deterioration in most of the tests, which has been paralleled by clinical deterioration. In particular, there has been a progressive reduction in the uptake of carbon monoxide. Our previous experience suggests that if this continues, he will very shortly develop cor pulmonale. Other cases have shown rather different findings. In some, all indices of function have

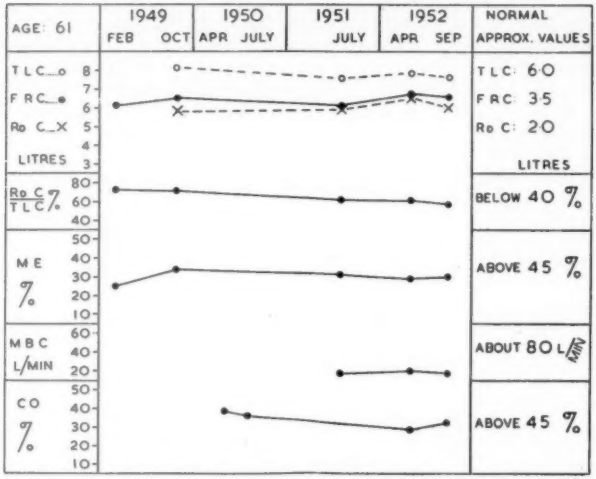


FIG. 1.—Lung function tests in a man aged 61 suffering from emphysema of moderate severity. TLC = Total lung capacity; FRC = Functional residual capacity; RdC = Residual capacity; ME% = Helium closed circuit index of mixing efficiency; MBC = Maximal breathing capacity; CO% = Percentage uptake of carbon monoxide. There has been little change clinically or functionally in the last three years.

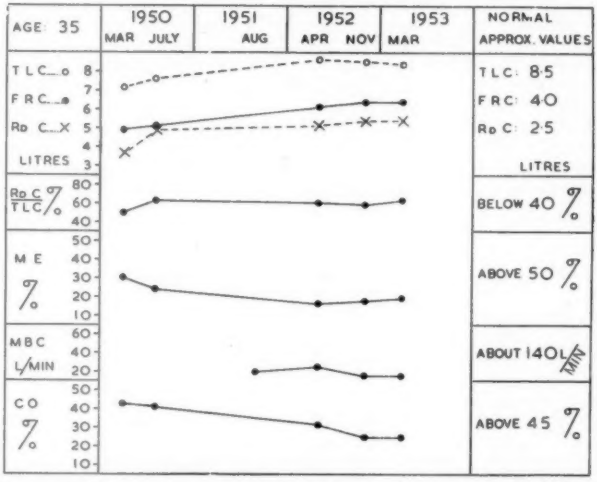


FIG. 2.—Lung function tests in a man aged 35 with severe emphysema. Abbreviations are the same as in Fig. 1. There has been progressive clinical deterioration over the last three years, and this has been accompanied by changes in the tests. In particular there has been a steady decrease in the rate of uptake of carbon monoxide. The vital capacity (TLC—RdC) has been almost constant at about 3 litres during the same period.

remained the same except that the fractional CO uptake has fallen fairly abruptly over the course of a few months, and in these cases cor pulmonale has developed when it has reached a low figure. Further work and observation is required before we will know precisely the mechanisms underlying these changes, and before we know the value of these different tests in prognosis.

SUMMARY

It is clear that a knowledge of the evenness of inspired gas distribution within the lung, together with a semi-quantitative estimate of the normality of blood gas interchange has contributed something and will undoubtedly contribute more to our understanding of lung function in a wide variety of conditions. These are still merely methods of research investigation, and, in my view, they are not

yet sufficiently precise or clear cut in interpretation to have much value in clinical practice, except perhaps in the elucidation of relatively rare conditions. One hundred years ago, John Hutchinson began the study of lung function tests by devising the measurement of vital capacity. The title of his paper reads: "On the capacity of the lungs, and on the respiratory functions, with a view of establishing a precise and easy method of detecting disease by the spirometer." Both "precision" and "ease" have proved difficult to achieve, but one day Hutchinson's objective will be reached—although I suspect that more will be required than just a spirometer.

BIBLIOGRAPHY

BATES, D. V. (1952) *Clin. Sci.*, **11**, 203.
COMROE, J. H. (1951) *Amer. J. Med.*, **10**, 356.
FOWLER, W. S. (1949) *J. appl. Physiol.*, **2**, 283.
RILEY, R. L., COURNAND, A., and DONALD, K. W. (1951) *J. appl. Physiol.*, **4**, 102.

Dr. C. M. Fletcher, Post-Graduate Medical School of London:

Function Tests and the Clinician

It is often felt that respiratory function testing will never descend from the laboratory to the clinic and become useful in the ordinary work of the clinician.

It is further maintained that such tests as the laboratory worker has hitherto devised have little relevance to clinical problems and are only useful in fundamental investigations into pulmonary physiology. It is this point of view which I now wish to discuss and I shall argue that, in fact, the clinician could derive considerable assistance from existing tests and is likely in the future to derive even more assistance from the newer tests.

The predominant symptom of disturbance of the function of the heart and lungs is undue shortness of breath on exertion and a common late sign of functional failure is cyanosis. Cyanosis is relatively easy to observe and although there is considerable error in clinical assessment of its severity its precise measurement in terms of oxygen saturation can be done by oximetry or by taking an arterial blood sample for gas analysis.

But the severity of exertion dyspnœa is not so easily assessed. This is a subjective symptom affected both by the patient's attitude towards his real or supposed disability, and by the amount of exercise which he is required to undertake in the course of his work. Subjective estimation of the severity of dyspnœa is therefore inevitably subject to considerable error and an objective method of measuring it would be preferable.

It is sometimes asked whether there is any practical importance in the measurement of exertion dyspnœa, more accurately than by simple clinical questions such as those which have formed the basis of clinical grading in cardiac and respiratory disease in recent years. I suggest that more accurate assessment of its severity is needed for the following clinical purposes:

(1) To distinguish between the increased awareness of normal exercise ventilation which anxiety may induce and a true impairment of ventilatory function.

(2) To provide objective measurement of the results of treatment.

(3) For assessment of disability benefit in industrial pulmonary disease and for assessment of capacity for jobs involving various levels of exertion.

It is necessary to measure two things in order to assess exertion dyspnœa. We have to measure both the ventilation required by the patient to achieve a given level of exercise and also his maximum ventilatory capacity, for it appears, in general, true that a sensation of breathlessness arises when the level of ventilation reaches 30–40% of the maximum ventilatory capacity. Thus, undue breathlessness on exertion may arise either from an increase in the ventilatory requirements on exercise or from a decrease in the maximum ventilatory ability, or from a combination of the two. To measure breathlessness, therefore, we must measure both exercise ventilation and maximum breathing capacity. Dr. McKerrow has dealt with methods of measuring the latter. Various methods are valuable for measuring the former. Expired air during a period of exercise may be collected in a Douglas bag and subsequently measured by passing it through a gas meter or, more simply, the expired air during a period of exercise may be passed through a gas meter and ventilation recorded minute by minute.

Some differences of opinion and practice exist concerning the type and amount of exercise that should be used. Some prefer the walking test, some the step test and some a bicycle ergometer. I prefer the step test described recently by Hugh-Jones, for a walking test is hard to standardize from one department to another unless a treadmill is installed, whereas the height of a step is easy to standardize and the rate of stepping can be regulated by a metronome. The bicycle ergometer is entirely satisfactory but some elderly patients may not take easily to it.

Differences of opinion also arise as to whether the work or the task imposed in the test should be kept constant. The answer here depends upon the purpose of the test. If we want to measure shortness of breath on walking or climbing stairs, then the task should be standardized so that heavier patients do more work than lighter patients as they do in everyday life. If we want to measure the effect of slimming on breathlessness we should certainly require to use a constant task. But if we want to measure the ventilatory response to a given increase of metabolic rate then the work should

be standardized. This would be necessary if we were studying the effect on respiratory function of increasing severity of a given disease or if we were studying the origin of dyspnœa in two separate diseases, such as heart failure or emphysema, for we should wish to rule out the irrelevant effect of the patients' weights. The simple step test can be used for standardized task or standardized work.

Having measured the degree of breathlessness, the next question the clinician must ask is why the patient is breathless. While in many cases the answer is clinically obvious there is not infrequently some real doubt. Often the doubt is only of academic interest and there is no clinical need for elaborate tests to clarify it, but occasionally guidance is required in respect of treatment and of prognosis. For instance, in a middle-aged man with a barrel chest, hypertension and auricular fibrillation who complains of shortness of breath, we may wish to know whether his shortness of breath is predominantly cardiac or respiratory in origin before we can prescribe the most useful form of treatment. Again the prognosis in a case of asthma may depend upon the severity of accompanying emphysema and a test which could distinguish between these two conditions may be of great help to the clinician. For this we require more elaborate tests, such as those to which Dr. Bates has referred. We need to choose some particular test that will enable us to discriminate between alternative functional diagnoses. This is a much better procedure than to call for a battery of all kinds of tests in the hope that something interesting may emerge.

Are such more elaborate tests really within the capacity of the ordinary clinician? Measurements of elasticity of the lung are hardly yet developed to the stage at which they can be interpreted as a routine and the exploration of intrapulmonary gas mixing and carbon monoxide uptake brings difficulties of interpretation. But the helium method of measuring lung volume, the maximum breathing capacity test, measurements of exercise and resting ventilation require relatively simple or purchasable apparatus and should be sufficient for many clinical purposes. It is still necessary for those who wish to use these tests to be able to call on some technical assistance in assembling and in operating the apparatus.

One further difficulty requires consideration, and that is the differentiation between a normal and abnormal test result. There is still far too little information available concerning the results of these pulmonary function tests in normal people of each sex at different ages. Until we know the range of variation in the normal population it is difficult to be sure when deviations from the normal occur. Too often a test is devised and tried out upon a small group of so-called "normals". The meaning of the word normal may range from supernormal athletes to hospital patients without respiratory disease. Comparison of test results in cases of respiratory disease with these two types of "normal" may result in widely divergent conclusions, especially if, as has been done, the effect of age upon respiratory function of normal people is forgotten.

There is one particular aspect of prognosis for which functional tests are commonly demanded and this is for the estimation of a patient's ability to withstand lung resection or other thoracic operations. We badly need much more information from follow-up studies after operation on patients who have been subjected to function tests pre-operatively before we can say which tests, if any, are likely to be of value in pre-operative prognosis. For this purpose we inevitably require methods for studying the function of local areas which are to be excised, whether a lobe or a whole lung. The separate study of each lung by bronchospirometry is a distressing and often difficult procedure although simplified by the Carlens catheter. Because of the obstruction to respiration, it is difficult to carry out studies except in the resting state, whereas we may wish to know the function of the lung on exercise. Further it is usually necessary for the patient to breathe oxygen throughout the study and the results thus obtained may not be relevant to the normal state of breathing air. For this reason the results of bronchospirometry may be misleading, but there is no doubt that in certain cases they may give a valuable indication of the normality of function of the lung that is to be retained after pneumonectomy, which may encourage or deter a surgeon.

Conclusion.—At present simple tests are available for the measurement of breathlessness and should be widely used, but the wider use of the more discriminatory diagnostic methods will have to await further research and standardization of equipment.

Dr. R. I. McCallum: Nothing has been said about the psychological effects of pulmonary function tests nor of the degree of co-operation necessary from the patient. In Newcastle we often see miners with radiological signs of pneumoconiosis who do not admit to any symptoms when their history is first taken. They are told the diagnosis and reassured, but frequently within a few months there is a deterioration in their condition and they complain of breathlessness. Either disability has been present from the first, or the breakdown is purely psychological in origin. A simple physiological test made at the time of the first physical examination before the patient knows the diagnosis, and repeated at intervals afterwards, would be invaluable. I would be interested to know whether lung function studies are likely to help in this problem and, if so, which type of test is most suitable.

Dr. M. C. S. Kennedy, Pneumoconiosis Research Unit, Llandough Hospital, Cardiff: My main interest is in the assessment of the bellows function of the lung since it is this component of pulmonary function that is most impaired in the majority of lung diseases. For this reason the assess-

ment of the ventilatory capacity by one method or another is a most useful measure, and one that has obviously come to stay.

Now the immediate question seems to be what method should be adopted for assessing this bellows function of the lung. The original method was described by Hermannsen in 1933, and consists of asking the patient to shift the greatest volume of air that he can in unit time; this flow rate is termed the Maximum Voluntary Ventilation (M.V.V.), which is synonymous with M.B.C.

I have carried out well over two thousand assessments of the M.V.V. using a low resistance spirometer, and found it to be a most fatiguing and time-consuming test to both patient and observer, and, further, if applied on an out-patient basis there is a considerable learning factor to overcome.

There is also the problem of how to standardize the rate of breathing whilst performing this test. A man who achieves an M.V.V. of 50 l./min., using a respiratory rate of 100 breaths per minute, is only moving $\frac{1}{2}$ litre per breath, of which roughly $\frac{1}{6}$ is dead-space air and functionless. Another achieves the same M.V.V. of 50 l./min., but uses a respiratory rate of 50 breaths per minute. This second man will be shifting one litre per breath, but only one-sixth of this volume will be functionless dead-space air. Obviously, although the two men produce exactly the same M.V.V. figure, physiologically the latter is better off, and under these conditions both are not being assessed on a comparable physiological basis. Add to this the inconsistency of M.V.V. values obtained in the same subject when he is to breathe at different respiratory rates (as shown by D'Silva and Mendel, 1950), and one is forced to the conclusion that the Maximum Voluntary Ventilation should be assessed as a fixed respiratory rate. Bernstein, D'Silva and Mendel (1952) have suggested that the M.V.V. be measured at a fixed respiratory rate. However, severely disabled patients cannot achieve a high respiratory rate and it is now advocated that patients be assessed at two or more respiratory rates. I do think the practical difficulties involved of increasing the number of measurements with a test that is already fatiguing and time consuming, preclude the adoption of this suggestion in all but academic work.

For these reasons, if the M.V.V. index is to be of use in routine clinical or survey work, we must have a simple, practical method of obtaining it. Because of this, I am interested in the assessment of the expiratory flow rate (E.F.R.), and I will briefly show, with the help of Figs. 1, 2 and 3, the test I employ.

Fig. 1 is a continuous tracing of a patient's resting respiration, followed by the quick expulsion of the whole of the vital capacity (E.V.S.) after a full inspiration. Next, he inspires his vital capacity (I.V.S.). Finally, the M.V.V. is shown using first a slow, and then a fast, kymograph speed. The tracing shows that the full inspiration or I.V.S. is virtually linear throughout its length. This has proved to be a common observation in many hundreds of tracings. However, the E.V.S. or expiratory curve is linear only throughout its upper part. Thus, if a man is to shift the greatest volume of air

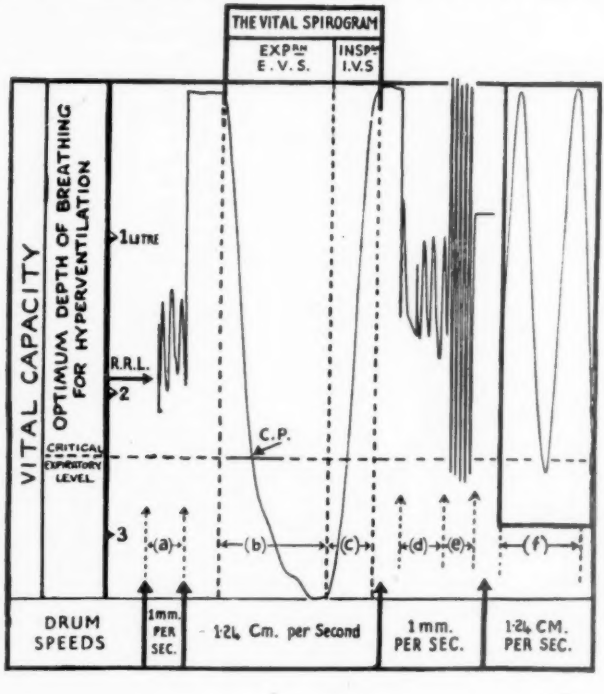


FIG. 1.—A continuous spirometer tracing using different drum speeds of (a) quiet breathing at rest, (b) a forced expiratory vital-capacity tracing or expiratory vital spirogram (E.V.S.), (c) a forced inspiratory vital-capacity tracing or inspiratory vital spirogram (I.V.S.), (d) quiet breathing + CO_2, (e) M.V.V. tracing, and (f) sample of an "optimum" M.V.V. tracing. C.P. = the critical point. R.R.L. = resting respiratory level.

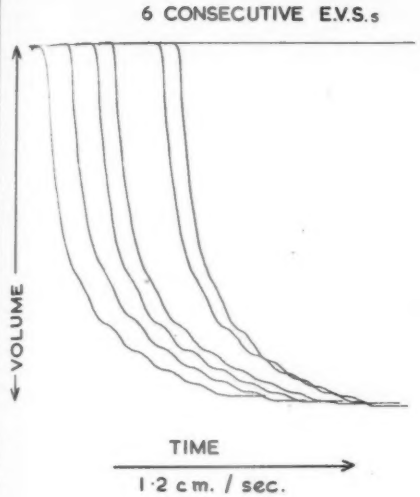


FIG. 2.

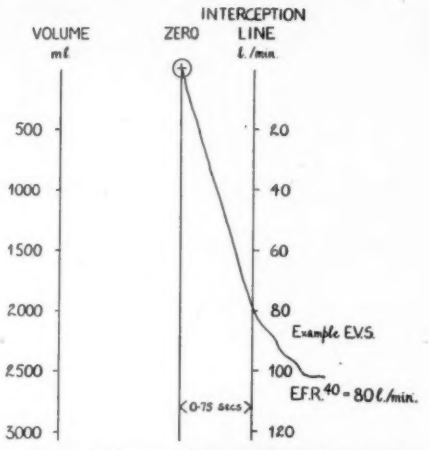


FIG. 3.—Diagram of the transparent protractor. Zero point in the centre of the circle is superimposed on the point of origin of the E.V.S. to be measured. The vertical lines on the protractor are next aligned with the true vertical lines on the tracing. The point where the E.V.S. cuts the intercept line gives the E.F.R.[40] of the E.V.S. (in the example above, the E.F.R.[40] is 80 l./min.). In practice the volume scale and the time scale would be graduated according to the volume of the spirometer and the speed of the drum periphery of the kymograph respectively.

(Figs. 1 and 3 are reproduced from *Thorax*, by permission of the Editor.)

per breath in the most efficient manner he will be using the upper linear part of his curve. The slope of the upper part of the E.V.S. curve mirrors very closely the expiratory phase of the M.V.V. This finding has been substantiated from many hundreds of tracings. From these two simple observations it would appear that a patient's M.V.V. can be assessed from the analysis of the volume of the upper linear part of the E.V.S. and the time-interval required to expel this volume.

If we fix the time-interval at 0·75 sec. which is equivalent to a theoretical breathing rate of 40 breaths per minute, hence the term E.F.R.[40], we find the correlation between this part of the curve and a patient's M.V.V. to be 0·93. The choice of this time-interval makes the absolute values of the M.V.V. and E.F.R.[40] very similar.

To obtain the E.F.R.[40], six consecutive E.V.S.s are recorded (Fig. 2) using a low resistance spirometer and a constant speed kymograph. I have used a spirometer similar to that made by Dr. J. C. Gilson.

Now each of the six curves is analysed separately using a transparent protractor as shown in Fig. 3. The centre of the zero circle is superimposed on the point of origin of the curve, and the E.F.R.[40] is read off where this curve cuts the ¾ second interception line. The mean of these six readings, corrected to 37° C. and saturated with water vapour, is taken as the E.F.R.[40] of the subject.

If we apply the criteria of a good test to this E.F.R.[40] measure we find the stability of this measure to be good, the standard error of 6 consecutive tracings is 2·4 l./min., which is less than the standard error of the M.V.V. test. The range of values extends from 10 to 180 litres of air per minute, which is very similar to the M.V.V. range. As regards validity, if the M.V.V. is valid then the E.F.R.[40] must be. Concerning the practicability of this test, in an out-patient clinic over 200 assessments are made each week by one charge nurse. Each assessment takes only two to three minutes.

Consecutive E.V.S.s in a co-operative patient are remarkably uniform and almost specific at any particular occasion, though, of course, they will vary from day to day if there are any changes in the factors influencing air flow. In long-term studies, qualitative as well as quantitative changes in the E.V.S. may well prove to be of diagnostic value. The E.V.S.s provide a permanent record, which gives a complete visual picture of the relative efficiency of any fraction of the vital capacity for hyperventilation.

BIBLIOGRAPHY

BERNSTEIN, L., D'SILVA, J. L., and MENDEL, D. (1952) *Thorax*, **7**, 255.
D'SILVA, J. L., and MENDEL, D. (1950) *Thorax*, **5**, 325.
GILSON, J. C., and HUGH-JONES, P. (1949) *Clin. Sci.*, **7**, 185.
HERMANNSEN, J. (1933) *Z. ges. exp. Med.*, **90**, 130.
KENNEDY, M. C. S. (1953) *Thorax*, **8**, 73.

LIST OF BOOKS RECEIVED FOR REVIEW

(As no reviewing is undertaken in the "Proceedings" this list is the only acknowledgment made of books received for review)

Grune & Stratton, Inc. (American publishers of the "Proceedings") "Timely medical books" (catalogue of publication), 1953. pp. 76. New York: Grune & Stratton. 1953.

Japan BCG Research Council. Studies on dried BCG vaccine. pp. 99. Tokyo: Japan BCG Research Council. 1952.

Ormerod (H. A.). The early history of the Liverpool Medical School from 1834 to 1877. pp. 52. Liverpool: University Press. 3s. 6d. 1953.

Samuels (J.). The pluripotency of the hypophyseal hormones: and the consequences for endocrinology and cancerology. pp. 296. Amsterdam: Cycloscoop. 37 guilders. 1953.

BOOKS RECENTLY PRESENTED AND PLACED IN THE SOCIETY'S LIBRARY

Alarcon Martínez (D. G.). Surgical extrapleural pneumothorax. pp. 297. Mexico: Imprenta Universitaria. 1948.

Arzt (L.), and Tappeiner (J.). Atlas der Haut- und Geschlechtskrankheiten. 2 vols. Plates. Vienna: Urban & Schwarzenberg. 1950–1953.

Denker (A. F. A.). Vergleichend-anatomische Untersuchungen über das Gehörorgan der Säugethiere nach Corrosionspräparaten und Knochenschnitten. pp. 114. Leipzig: Veit. 1899.

Flatau (E.). Atlas of the human brain and the course of the nerve-fibres. pp. 25. Berlin & Glasgow: Karger & Bauermeister. 1894.

Kazancigil (T. R.). Diagnostic histopathologique en gynécologie. pp. 189. Paris: L'Expansion Scientifique Française. *c.* 1953.

Lees (J. C.), and Lees (T. W.). The treatment and classification of cancer. pp. 63. Edinburgh: Oliver & Boyd (for private circulation). 1952.

Lisbon University. Faculdade de Medicina. Biblioteca. Catálogo das obras da colecção portuguesa de 1825 à 1910. pp. 545. Lisbon: Garcia & Carvalho. 1952.

Ormerod (H. A.). The early history of the Liverpool Medical School from 1834 to 1877. pp. 52. Liverpool: University Press. 3s. 6d. 1953.

Power (Sir D'Arcy), and Waring (Sir Holburt J.). A short history of St. Bartholomew's Hospital, 1123–1923. pp. 201. London: St. Bartholomew's Hospital. 1923.

Samuels (J.). The pluripotency of the hypophyseal hormones: and the consequences for endocrinology and cancerology. pp. 296. Amsterdam: Cycloscoop. 37 guilders. 1953.

Section of Dermatology

President—G. B. DOWLING, M.D., F.R.C.P.

[*January* 15, 1953]

Sclerema Neonatorum.—R. T. BRAIN, M.D.

The patient, H. S., was a female infant aged 5 weeks when brought to the Hospital for Sick Children, Great Ormond Street. She had been a full-term baby delivered after a normal labour lasting about seven hours and the birth-weight was 8 lb. The mother's pregnancy had been uncomplicated and it was unlikely that she had had any dietary deficiencies. About the third or fourth day of the infant's life an extensive dusky bluish area was noticed on the back, extending from the lower rib margins to the base of the neck and in the lower part of this area two large swellings were observed (Fig. 1). The infant was breast fed and her general condition and nutrition were good.

FIG. 1.—H. S., aged 6 weeks, showing two cystic swellings.

Examination.—The infant was sturdy and healthy and the only abnormal feature was that the skin across the back and shoulders was of a brownish-red colour with an irregular nodular surface, here and there causing coarse creases near the edges. In the lower part on each side of the mid-line were two soft fluctuating communicating cysts 3–4 cm. in diameter. When the centres of these soft swellings were depressed with the fingers, a firm collar of indurated subcutaneous tissue was felt to surround the base of each. This induration was continuous over the affected area and resembled a waxen plaque approaching 1 cm. in thickness. It was possible to insert the finger-tips beneath the well-defined edges, especially near the neck, and it seemed that the induration involved the hypoderm. The skin was firmly attached to it but was otherwise relatively normal in texture.

On aspiration of the cyst a thick creamy sterile fluid was obtained containing no cells but only fat droplets and doubly refractile crystals.

X-ray of soft tissues showed no calcification.

Biopsy.—The fat excised from the affected area was hard, opaque, white and avascular. Sections (Dr. M. Bodian): "The cutis shows only minimal changes, slight œdema and very little cellular infiltration. There is some variation in the size of fat cells which have, on the whole, preserved their outline. Needle-like crystals lie in the fat (and some outside) mostly in radiating tufts and some singly. Whenever they lie outside the cells they are colourless but within the fat cells they appear to take up the stain for neutral fat; this, however, is probably spurious. A granulomatous infiltrate in the fibrous septa around the fat lobules spreads also into the lobules. This consists of histiocytes, lymphocytes and polymorphonuclear leucocytes, but foreign body giant cells are also present in apposition to some of the fat cells."

Comment.—I reported a very similar case in 1947 but no cystic lesions were present. Resolution in that instance was almost complete in two months.

The special interest of this case is in the two fluctuant swellings over the mass. Such swellings are distinctly rare although Sir Archibald Gray's (1926) first two patients showed them. They may be mistaken for abscesses or cavernous hæmangiomata.

No notable contribution has been made since the work of Channon and Harrison (1926) on the chemistry of the fat. The conclusion was that there was a relative deficiency of olein so that the preponderance of stearin and palmitin gave a high melting point to the body fat and that, possibly, cooling of the skin led to the deposition of needle-like crystals which provoked a foreign-body granulomatous reaction. Although the investigations of Harrison led to the inference that the crystals were natural fat, neither the evidence nor the explanation was entirely satisfactory since in view of the fact that an infant's fat contains less olein than that of an adult, it is surprising that sclerema neonatorum occurs so rarely and is not much more common in cold climates.

The differential diagnosis involves the separation of this specific entity from œdema neonatorum, scleroderma, pre-agonic or cadaveric induration of the fat of the newly born and possibly from what is described as subcutaneous fat necrosis of the newly born. One would expect subcutaneous fat

necrosis to be localized and usually traumatic but, whether traumatic or idiopathic, saponification of the necrotic fat tissue would result in the early formation of free fatty acids and deposition of calcium salts. Harrison was unable to find free fatty acids in his investigations of material from sclerema neonatorum. Pre-agonic or cadaveric induration is so obviously an ante-mortem solidification of the fat in a marasmic, moribund infant that it could scarcely be confused with sclerema neonatorum, except in the rare case when the latter disease involves the trunk and limbs with, in consequence, a serious prognosis.

I am indebted to Dr. C. H. Whittle and to Dr. O. P. Bewers, the attending practitioner, for this interesting patient, and to Mr. D. Martin for the excellent photograph.

After showing a photograph of his case, Dr. Brain showed a second photograph and said that it illustrated the patient he saw with Dr. E. Davis in 1945. The clinical condition was very similar to that of the patient shown to the meeting but no cysts were present (*see* Davis and Brain, 1947).

POSTSCRIPT (June, 1953).—Progress: The condition had clinically resolved in two months. **R. T. B.**

BIBLIOGRAPHY

CHANNON, H. J., and HARRISON, G. A. (1926) *Biochem. J.*, **20**, 84.
DAVIS, E., and BRAIN, R. T. (1947) *Brit. J. Derm.*, **59**, 312.
GRAY, A. M. H. (1926) *Arch. Derm. Syph., Chicago*, **14**, 635.
—— (1933) *Brit. J. Derm.*, **45**, 498.
HARRISON, G. A. (1926) *Arch. Dis. Childh.*, **1**, 63 and 123.

Urticaria Pigmentosa with Bone Lesions. Two Cases.—C. D. CALNAN, M.B.

I.—K. P., female, aged 24.

History.—Three years ago: Onset of eruption on legs and arms, and some lesions scattered on trunk. They become red and wheal with friction or heat.

Examination.—The arms, legs and chest show urticaria pigmentosa of the adult type.

Investigations.—Biopsy: Numerous mast cells in the dermis, especially around blood vessels. X-ray of skull: There is an annular clear-cut deficiency about 1 cm. diameter of both tables in the L. parieto-frontal region in the line of a suture. The margins are sclerosed (Fig. 1).

II.—E. F., female, aged 52.

History.—Five years: Rapid onset of the present eruption which itches on occasions especially when the skin is exposed to a fire or hot water. It is present on the arms, legs and more sparsely on the trunk.

Examination.—Lesions of urticaria pigmentosa of adult type on the forearms, arms and lower legs, and a few on the trunk.

Investigations.—X-ray skull: There is a small ill-defined defect in the right frontal bone about 5 mm. diameter (Fig. 2).

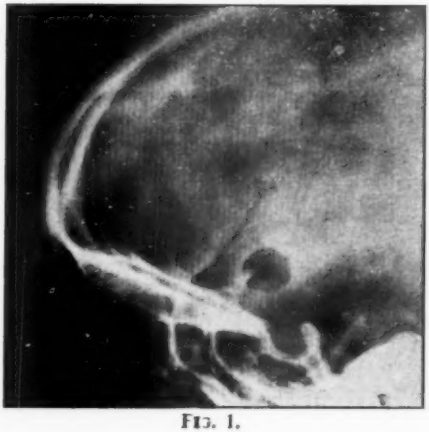


FIG. 1.

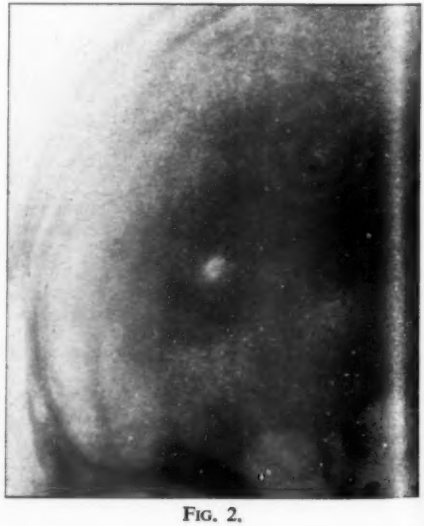


FIG. 2.

Comment.—These 2 cases are presented in order to discuss the significance of bone lesions in urticaria pigmentosa.

I became interested after reading of Felix Sagher's patient who had cystic osteoporosis of the ribs and vertebræ (Sagher *et al.*, 1952). (Clyman and Rein, 1952, also have examined about 6 patients.) There is no specific diagnostic feature about the X-rays of my patients, and the abnormalities could well be due to other incidental pathological processes. There is, however, some evidence for regarding this condition as a systemic disorder, and French authors not infrequently classify their cases as mast-cell reticulosis (Hissard *et al.*, 1951).

REFERENCES

CLYMAN, S. G., and REIN, C. R. (1952) *J. invest. Derm.*, **19**, 179.
HISSARD, R., MONCOURIER, L., and JACQUET, J. (1951) *Presse méd.*, **82**, 1765.
SAGHER, F., COHEN, C., and SCHORR, S. (1952) *J. invest. Derm.*, **18**, 425.

Congenital Ichthyosiform Erythrodermia (Brocq) with Bullæ.—R. G. HOWELL, M.R.C.P. (for H. J. WALLACE, F.R.C.P.).

R. W., male, aged 23.

This patient shows the characteristic lesions of congenital ichthyosiform erythrodermia, with large plaques of horny skin on the trunk and limbs. The face and extremities are less markedly involved. The lesions have remained unchanged since early childhood. On the trunk and legs he develops bullæ, 2·5–5 cm. in diameter. They are flaccid, subepidermal, and readily become secondarily infected. There is no seasonal incidence.

Treatment.—Liquid paraffin is the most suitable local application. Vitamin A, 150,000 units daily for nine months, made no change to the lesions. Sulphapyridine, 0·5 gramme t.d.s., appears to reduce the frequency of blister formation.

Comment.—The occurrence of bullæ in this disease has been attributed to sepsis, to sweat retention and to trauma. Sulphapyridine may have some effect if sepsis is causative.

Partial Congenital Ichthyosis.—R. G. HOWELL, M.R.C.P. (for G. B. DOWLING, M.D., F.R.C.P.).

J. K., male, aged 38.

This patient has had thickening and roughness of the skin of the arms and legs since infancy.

The lesions are symmetrical and involve the dorsum of the hands and feet, the arms to above the elbows and the legs to the mid-thigh. There is a sharp line of demarcation between affected and normal skin and there are bilaterally symmetrical islands of normal skin in the hyperkeratotic areas. The palms and soles are not affected. The lesions are symptomless and do not vary.

Comment.—This case resembles that described by Vilvandré as "an unusual case of symmetrical keratodermia". In both cases the lesions are symmetrical, sharply demarcated from normal skin, and remain unchanged from early childhood. In Vilvandré's case the hyperkeratosis was more florid, and the palms and soles were involved.

REFERENCE

VILVANDRÉ, G. (1918) *Brit. J. Derm.*, **30**, 202.

Dr. H. J. Wallace: There is one detail I would like to add. The cause of the blistering in the patient is uncertain but we have another patient with a less severe form of this disorder in whom the blistering invariably appears to be traumatic.

Dr. H. R. Vickers: I would suggest that the second case is of the same order as the first. I do not like the diagnosis of ordinary ichthyosis; there is no involvement of the palms.

Dr. R. T. Brain: I agree. One can see the exaggerated pattern of hyperkeratosis in both cases. I think this may have started as a congenital ichthyosiform erythrodermia. The erythrodermia disappears and leaves the ichthyotic elements which become more conspicuous.

Dr. F. Ray Bettley: I think the second case would be best called widespread hyperkeratotic nævus because it does not really have the characteristics which are present in the first case which is a true congenital ichthyosis, with extremely thick "crocodile" skin. The second case does not progress to that degree.

Sarcoid Following Injury.—R. G. HOWELL, M.R.C.P. (for G. B. DOWLING, M.D., F.R.C.P.).

M. F., male, aged 32.

This man was blown up by a "booby-trap" in Palestine in 1945. His face and shoulders were peppered with soil particles. When seen in 1951 there were many small brown-red papules scattered among the black pigmented marks of his injuries. He could not say when the nodules first appeared, and they have remained unchanged since 1951. The spleen was not palpable and there were no enlarged lymph glands. The general health was good.

Investigations.—X-ray of chest and hands revealed no abnormality. Mantoux 1/1,000 negative.

Biopsy of a nodule from the shoulder (Dr. Ian Whimster).—"The dermis contains numerous discrete and confluent tubercles. Doubly refractile, colourless, crystalline foreign bodies are present in the tubercles, sometimes inside giant cells, but are also present in the dermis where they do not appear to be exciting any inflammatory reaction."

Treatment.—Foreign bodies have been removed from both eyes and a right corneal graft done. No treatment has been given for the skin lesions.

Comment.—Silica particles in the skin may excite a particular "tuberculoid" local inflammatory response, or if the patient develops "sarcoidosis" subsequent to the injury, the silica particles may preselect the site of the lesions.

In R. D. Sweet's case, sarcoid tissue was found in lymph glands quite independent of silica deposits. Silica particles in the skin are only rarely associated with "sarcoid" tissue. It appears then that they may preselect the sites of development of lesions in a generalized disease.

REFERENCE

SWEET, R. D. (1950) *Proc. R. Soc. Med.*, **43**, 173.

The following cases were also shown:

Scleroderma.—Dr. C. H. WHITTLE and Dr. J. MOFFATT.

Granuloma of Face: For Diagnosis.—Dr. G. A. BECK and Dr. C. H. WHITTLE.

Case for Diagnosis: ? Granulomatous Mycosis. ? Squamous Carcinoma.—Dr. BRIAN RUSSELL.

Epidermolysis Bullosa Dystrophica.—Dr. P. J. FEENY.

Hypertrophic Lichen Planus with Epitheliomata.—Dr. HAROLD WILSON.

(These cases may be published later in the *British Journal of Dermatology.*)

[*February* 19, 1953]

Mycosis Fungoides.—I. B. SNEDDON, M.B., Ch.B., M.R.C.P.

A. W., male, aged 66. Monumental Mason.

History.—In October 1952 he developed an itching red eruption on the head, face and neck and his face became swollen. Apart from this he felt well; he had taken no drugs. The rash had spread slowly down his trunk and the proximal parts of the limbs.

Past history and family history.—Not relevant.

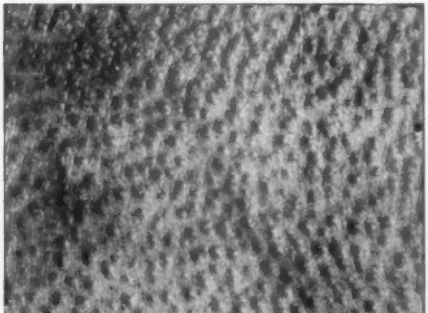


FIG. 1.—The skin of the upper trunk showing the follicular papular eruption.

On examination.—A confluent bright erythema was present over the scalp and face; the skin of the face was indurated and deep fissures were present in the natural skin folds around the mouth. The neck, upper trunk and arms showed a discrete red follicular papular eruption which was becoming confluent around the neck (Fig. 1). The hands and feet were unaffected. No enlargement of lymph glands, liver or spleen could be found.

Investigations.—Skiagram of chest showed no significant abnormality. W.R. negative. Blood count: Hæmoglobin 128%; red cells 6,400,000; leucocytes 9,000; differential count normal; marrow puncture within normal limits.

Histological examination of the follicular rash on the trunk (Dr. L. C. D. Hermitte): The epidermis shows a slight degree of acanthosis. Its surface is wavy but there is no hyperkeratosis or parakeratosis. The mouths of the follicles are, however, filled with lamellated keratin. There is a dense perifollicular infiltrate with lymphocytes and histiocytes and the centre of the follicle appears to contain keratin. The sebaceous glands show some degree of atrophy. Some of the capillaries in the corium are dilated and surrounded by a few chronic inflammatory cells. The appearances suggest a mild degree of pityriasis rubra pilaris.

FIG. 2.—Section of facial skin. × 43.

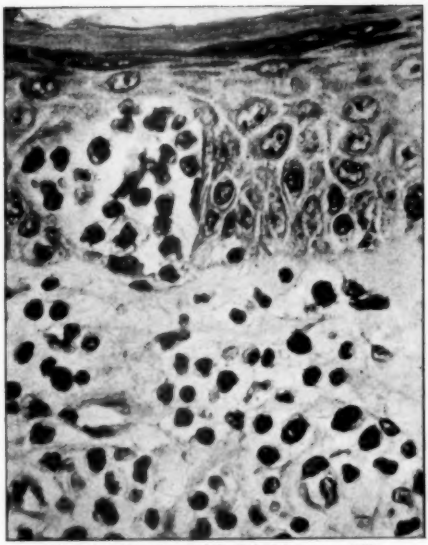


FIG. 3.—Section of facial skin. × 460.

Histological examination of the skin of the face (Figs. 2 and 3) shows œdema and degeneration of the corium which is densely infiltrated with round cells. This infiltrate is pleomorphic in character. Some of the cells are small with dark nuclei, others are larger with pale nuclei, many showing mitotic figures. These cells appear to be reticulum cells. The infiltrate has invaded the epidermis in several places. The appearances are those found in a malignant reticulosis.

Comment.—Although the infiltrate does not show a great deal of pleomorphism its diffuse arrangement and the clinical picture of a reticulosis so far confined to the skin suggests a diagnosis of mycosis fungoides in the erythematous and infiltrative stage. That mycosis fungoides can present with a seborrhœa-like eruption is well known but that it can simulate pityriasis rubra pilaris so closely has not, so far as I know, been described. I have watched a similar case for five years; this case has been controlled with cortisone 250 mg. daily for two years. He has never shown any evidence of systemic involvement nor has the large dosage of cortisone had any apparent harmful effect.

The President: The diagnosis of a reticulosis appears to be beyond dispute but I do not believe that the skin reticuloses presenting as a diffuse erythrodermia are as yet accurately sorted out. Mycosis fungoides may perhaps not be the correct term for this case.

Dr. Sneddon, in reply to a question: In my previous case, X-rays had no beneficial effect and in the present case a total of 450 r has been given to the right side of his face without any benefit.

?Purpura Urticans with Regional Distribution (Early Manifestation of Vascular Sensitization) and Polyarthritis. Case for Diagnosis.—L. FORMAN, M.D.

M. R., female, aged 43.

October 1950, small urticarial papules appeared over the ankles and have since involved the legs, thighs, buttocks, face, the exposed part of the chest, the hands and arms. She has always had a high facial colour but during the past few years the colour has deepened and telangiectasia of the face and of the chest wall is more obvious. Over the areas affected red macules appear which quickly become urticated to form prominent white papules of a diameter of 1 cm., showing a central red punctum, presumably a dilated capillary. They do not itch but burn and are slightly tender to touch. After two to three days the papules subside leaving a brown stain which may take up to a week to disappear. All stages are to be seen on the limbs. There has also been an associated periodic swelling and pain of the hands with some tenderness of proximal joints of the thumbs and swelling of the ankles, knees and elbows. The number of papules are increased before the period is due. She was put in bed in hospital and obtained much relief. While at rest in bed the number of papules and their duration has diminished. Cold and fatigue, she believes, increase the number of papules.

Investigations.—Effect of cold: Hand immersed in cold water (16° C.) for ten minutes: numerous papules developed on the hand and on the arm; during the next three hours all finger joints swelled and numerous papules appeared on the arms and legs.

Effect of heat: Feet immersed in hot water for ten minutes: no effect on papule formation.
Histamine scratch produced a flare and also a flare around papules 2 cm. away. The reaction lasted for three hours. (Reaction in control normal individual lasted twenty minutes.)
Electrophoresis with 0·05% carbachol showed greater sensitivity than normal.
No cold agglutinins were detected in the blood.
No urinary porphyrins, bone-marrow normal, no L.E. cells.
Blood count normal. W.R. negative.
Blood: congo red elimination test within normal limits.
Serum cholinesterase within normal range.
In 1951 there was dental sepsis of the upper teeth with alveolar loss. This was treated.
Biopsy of a papule: Dilatation of superficial capillaries with œdema. The cellular exudate consists of pyknotic polymorphs and a few histiocytes and eosinophils and red cells. ? Homogenisation of subepithelial layer of deeper vessels.

Treatment.—Antihistamines and elimination diets without avail.

Comment.—The recurrent urticarial wheals, with residual staining probably due to the diapedesis of red cells seen in the section, and the recurrent transient peri-articular swelling suggest an allergic reaction. No food or drug allergens could be detected. The superficial capillaries may be the site of sensitization. At the moment there is no sign of vascular damage to larger blood vessels or to the renal blood vessels. The biopsy with its large number of polymorphs suggesting an abscess, recalls the histology of erythema elevatum diutinum which, as has been shown, is associated with degenerative changes in the skin blood vessels.

Addendum (10.4.53).—She had ACTH gel 20 mg. a day for seven days intramuscularly and then ACTH 20 mg. a day intravenously for seven days and the third week she was given ACTH gel intramuscularly 20 mg. per day for seven days. During the course of treatment the patient had no further swelling of the joints, the maculo-papular rash gradually disappeared and the duration of the papules was limited to six hours; there was no subsequent pigmentation. The venous congestion of the face and chest also diminished. She has been observed for the past two weeks, since the cessation of treatment, and she has again developed a few small papules on the limbs.

Dr. H. Haber: The histology reminds me of the case which Dr. Brian Russell and I showed at the R.S.M. (1950, *Proc. R. Soc. Med.* **43**, 560). I would regard that condition as belonging to the group of Erythema Elevatum Diutinum. The perivascular infiltration consisting of polymorphs and a few eosinophils with very little degeneration of the cells is unique and characteristic of erythema elevatum diutinum as outlined by Weidmann.

The following cases were also shown:

Dermatofibrosarcoma Protuberans.—Dr. E. WADDINGTON,
(This case will be published in the next issue of the Section of Dermatology.)

Widespread Morphœa with Bullæ and Leukoplakia.—Dr. R. E. CHURCH (for Dr. I. B. SNEDDON).

Chloasma Treated with Monobenzyl Ether of Hydroquinone.—Dr. L. FORMAN.

? Secondary Carcinoma. ? Amelanotic Melanoma.—Dr. S. C. GOLD.

Parakeratosis Variegata with Unusual Features.—Surg. Lt.-Cdr. R. SCUTT.

Reticulosis Cutis.—Dr. N. A. THORNE (for Dr. BRIAN RUSSELL).

Syphilitic Leukoderma of the Neck.—Dr. C. S. NICOL.

Congenital Progressive Cutaneous Atrophy with Bullous and Poikiloderma-like Manifestations.—Dr. THERESA KINDLER.

Familial Benign Pemphigus.—Dr. C. D. CALNAN.

Two Cases of ? Pigmented Purpuric Lichenoid Dermatitis (Gougerot and Blum).—Dr. B. SCHWARTZ.
(These cases may be published later in the *British Journal of Dermatology*.)

[*March* 19, 1953]

The following cases were shown:

(1) Persistent Peri-orbital Œdema. (2) Ungual Dystrophy. ? Lichen Planus.—Dr. J. OVERTON.

Atypical Granuloma Annulare in a Diabetic.—Dr. G. A. BECK (for Dr. C. H. WHITTLE).

Recurrent Painful Swellings of Shin—For Diagnosis.—Dr. A. JARRETT (for Dr. W. N. GOLDSMITH).

(1) Arsenical Keratoses and Pigmentation. (2) Paraffinoma. (3) Lichen Nitidus.—Dr. C. D. CALNAN.

Cheilitis Glandularis Apostematosa.—Dr. E. WADDINGTON.
(These cases may be published later in the *British Journal of Dermatology*.)

Section of Urology

President—J. G. YATES-BELL, M.B., F.R.C.S.

[*January* 22, 1953]

SYMPOSIUM ON BLADDER-NECK OBSTRUCTION

Clinical Aspects and Pathology of Bladder-neck Obstruction

By J. P. MITCHELL, F.R.C.S.
Bristol Royal Infirmary

and G. S. ANDREWS, M.D.
Dept. of Pathology, Bristol General Hospital[1]

Mr. J. P. Mitchell: Obstruction at the outlet of the bladder can occur at all ages and in both sexes. This obstruction is a separate entity from adenomatous hyperplasia of the prostate, though the two conditions can occur simultaneously in the same patient. We have seen it in the neo-natal period which leads us to believe that it is a true congenital abnormality and we suggest that a familial incidence may sometimes be found.

This condition has in the past been recognized and described by many observers under many different names. (The works of Guthrie, Mercier, Herbst and Marion were described.)

The purpose of this paper is to quote examples of the condition as it has been encountered in all age groups and in both sexes, and attempt to show that the underlying pathological process is the same in all groups. It is possible in this way to build up a life history of the lesion.

The clinical findings vary with the age of the patient and the severity of the condition when the patient is first seen. In the first stage the symptoms may be merely a disturbance of micturition, such as enuresis in children, or frequency and urgency in adult life. With only slight obstruction the consequent hypertrophy of the wall results in a hypertonic bladder of small capacity. As the condition progresses urine is retained in ever-increasing quantities until ultimately a state of chronic retention with overflow incontinence is reached, or acute retention supervenes. This is regarded as the second stage. Finally, the chronically distended bladder may cause back-pressure on the ureters and kidneys, followed by hydronephrosis and the beginning of renal failure. The upper urinary tract may, however, be saved by the formation of a diverticulum through the hypertrophied bladder wall. Though the diverticulum acts as a safety valve against damage to the kidneys, it carries with it the added risks of infection and stone formation.

If the urine becomes infected at any stage in the progress of the disease the symptoms may be modified, in fact some patients have presented merely with recurrent attacks of cystitis or pyelitis.

73 cases have been examined and treated in the Urological Unit at Bristol during the past two years. No case was included in this series if any of the following features were present:

(1) Any significant prostatic enlargement palpable on rectal examination.
(2) Any evidence of malignancy either clinically or histologically.
(3) Any neurological signs which might account for a neurogenic disturbance of bladder function.

Also included in this series are 6 patients in whom the bladder-neck obstruction followed an open operation for prostatectomy. Cases were shown to have occurred in every decade of life with the peak incidence between 45 and 55 years of age.

In the neo-natal period and in infancy the condition is seldom recognized unless acute retention occurs or the child is found to have a distended abdomen caused by a full bladder. One male infant was stated by the parents to go twenty-four hours without passing water, but what brought them to the doctor was the apparent straining and the crying just before micturition.

After the age of 5 the condition may be found as a result of investigations for enuresis. In a small percentage of enuretics there is a true organic basis, of which bladder-neck hypertrophy is one. It is as though the hypertonic bladder of small capacity is unable to stretch beyond a certain limit and automatic evacuation occurs which overcomes all normal inhibition of micturition. The usual history obtained in these cases is that the child was dry by night as well as by day from the age of 3 or 4 years, but after two or three years dry, the child again relapses into enuresis. 4 girls in this group gave histories of recurrent attacks of severe urinary infections, and in all 4 patients no further attacks of urinary infection have occurred since the bladder neck was resected transurethrally.

The child with slight obstruction proceeds to adult life with only slight disability. After puberty, enuresis disappears but frequency and some urgency remain throughout life. These patients will say that they have always had a small bladder. They may complain of difficulty and a poor stream with occasional attacks of pain on micturition. All the patients in the first two decades of adult life gave histories of enuresis in childhood until puberty.

[1]Now at St. Woolos Hospital, Newport, Mon.

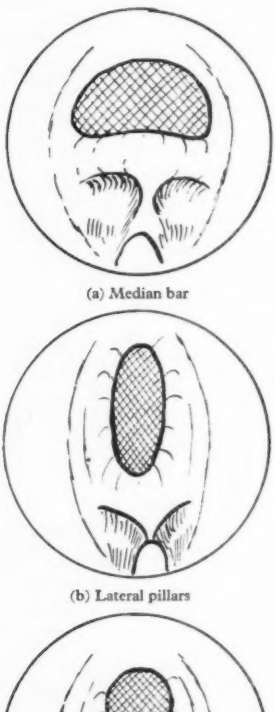
In the later age groups frequency is still the commonest symptom, though a form of incontinence reappears. In 6 cases this was a true incontinence severe enough to be very distressing to the patient, but in others it was an indication of chronic retention. Acute retention brought 8 patients into hospital as emergencies. In one patient investigation for hæmaturia revealed a large infected diverticulum.

The patient may reach the prostatic age group before his symptoms really inconvenience him. At this age and with no clinical or cystoscopic evidence of benign prostatic enlargement, this condition has been given the term "prostatisme sans prostate".

In the female adult the symptoms are increasing difficulty culminating in acute or chronic retention. Infection is even more liable to occur than in the male and is usually of a more intractable nature.

To investigate these cases cystoscopically it is essential to use an irrigating cysto-urethroscope of the Brown-Buerger or Millin type. On introducing the cystoscope, difficulty may be encountered as the beak reaches the bladder neck, and often the shaft of the instrument has to be dipped considerably before it will pass on into the bladder.

At the bladder neck some degree of thickening may be seen, but the localization of this thickening appears to vary. In some it extends from four to eight o'clock posteriorly forming the classical median bar (Fig. 1a). In others, particularly children, it may be localized laterally at three and nine o'clock forming a pillar on each side of the bladder neck (Fig. 1b). In the majority of cases a collar of thickening exists around the entire circumference of the internal urinary meatus (Fig. 1c).



(a) Median bar

(b) Lateral pillars

(c) Collar thickening

FIG. 1.—The appearances of the internal urinary meatus when viewed from the posterior urethra at the level of the verumontanum.

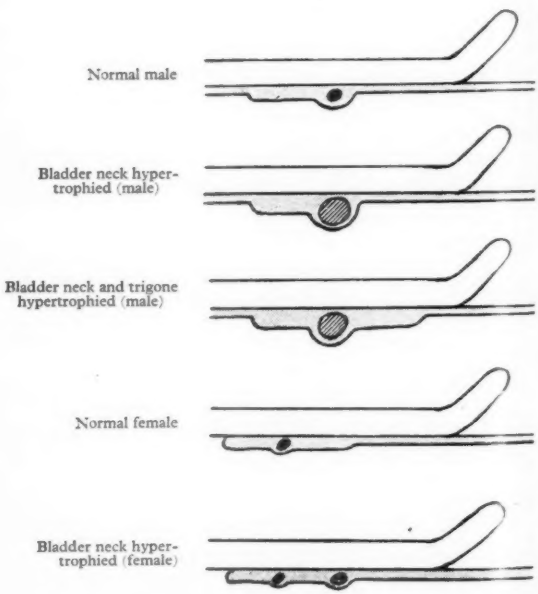


FIG. 2.—The amount of tissue felt between the examining finger *per rectum* and the cystoscope at the bladder neck.

When the neck is hypertrophied the run into the bladder is often a steep drop down on to the trigone, but if there is hypertrophy of the trigone itself this steep drop is smoothed out. As the cystoscope is withdrawn into the prostatic urethra a pouch is usually seen posteriorly just distal to the internal urinary meatus and immediately above the verumontanum.

One useful diagnostic sign is obtained with a finger *per rectum* at the time of the cystoscopy. The amount of tissue felt between the examining finger and the cystoscope at the bladder neck is usually a guide to the degree of hypertrophy. The diagrams (Fig. 2) show firstly the normal adult male. A thickening can be felt running across the cystoscope in the region of the neck of the bladder and in the centre of this thickening is a small firm core. Distal to this is the soft prostatic tissue and the thin membranous urethra. If the bladder neck is hypertrophied, then the thickening felt will be as much as the size of one's little finger with a firm core almost as large. Usually a very marked change is noticed from the bladder wall, through which the cystoscope is easily palpable, to the indurated neck, but this again may be smoothed out if there is hypertrophy of the trigone. The normal female differs in that no firm core can be felt at the neck; any thickening is therefore pathological. There is, however, a thin band palpable about 1 cm. proximal to the external urinary meatus, and this corresponds to the external sphincter of the urethra.

Cystoscopically the patients appeared to fall into four groups (Table I). Group I is merely an age group. Group II consists of cases of bladder-neck obstruction without any cystoscopic evidence of

TABLE I.—CLASSIFICATION ON CYSTOSCOPY

		Number of patients
(I)	Occurring in children or young adults (under 20 years of age)	16
(II)	Median bar, lateral pillars or collar thickening	
	(A) No evidence of infection	22 } 38
	(B) Urine found to be infected	16 }
(III)	Cystoscopic evidence of early prostatic hypertrophy	13
(IV)	Post-prostatectomy obstruction	6
	Total	73

prostatic enlargement. Group III includes all those cases showing any suggestion of lateral or middle lobe enlargement of the prostate on cystoscopy despite the rectal findings of a gland within the normal limits of size. All post-prostatectomy bladder-neck obstructions were placed in Group IV. In view of Marion's theory that chronic infection is an ætiological factor in this disease, it was decided to subdivide Group II into those with no previous urinary infection (Group IIA) and those in whom there was evidence of chronic infection (Group IIB). Table II shows the average age of the patients in these

TABLE II.—AGE AND LENGTH OF HISTORY

		Average age of patient in years	Average length of history in years	Number with disturbance of micturition in infancy
(I)	Occurring in young adults and children	10	6	—
(II)	Median bar, lateral pillars or collar			
	(A) No evidence of infection	48	9	11
	(B) Evidence of chronic infection	58	4	2
(III)	Cystoscopic evidence of early prostatic hypertrophy	61	1½	None
(IV)	Post-prostatectomy obstruction	65	1½	None

groups, with the average length of history and the number of patients from whom there was a history of micturitional disturbance in infancy. As would be expected, those patients showing evidence of early prostatic hypertrophy were of a higher age group, the length of history was shorter and there was no previous history of trouble in infancy.

The indications for surgical treatment were either the presence of complications such as hydronephrosis, diverticulum or chronic retention of urine, or the distressing nature of the symptoms in the earlier stages of the disease. Transurethral resection, using a valve machine for the cutting current, was the method of choice in the majority of the cases. The extent of the resection necessary was judged from the appearance of the bladder neck, which opens out into a funnel immediately an adequate amount of tissue has been resected. In view of the narrow margin of error a finger *per rectum* is an essential in the final stage of resection. In the very young the urethra will not accommodate the child's resectoscope even with a perineal urethrostomy and a transvesical approach was used, a cuff of tissue being excised from the bladder neck by scissor dissection. The transvesical approach was also used in the event of additional intravesical pathology such as stones or diverticula. However, it was felt that a more accurate clearance was obtained with the resectoscope than by open operation.

In as many cases as possible the chippings were orientated according to the part of the bladder neck from which they were resected. Attempts were made to obtain pieces from one o'clock, three o'clock

and six o'clock and each of these was preserved independently for histology. The total weight of tissue resected in each adult was between 7 and 11 grammes.

The results, if successful, are immediate and dramatic but if unsuccessful then little further improvement has been noticed after three months. Out of 73 patients, 59 have been considerably improved.

Finally, I would draw attention to the high incidence of this condition. That 73 cases should have been collected in Bristol during the past two years is possibly a little misleading as many of them have been referred from various parts of the South West Region and from other consultants in Bristol. Nevertheless, this disease is far from uncommon. The recognition and treatment of bladder-neck obstruction in childhood will relieve some enuretics and will delay or even prevent the onset of symptoms at a later age when the condition would otherwise be more advanced.

My thanks are due to Mr. Ashton Miller for permission to include a large number of his cases in this series.

BIBLIOGRAPHY

GUTHRIE, G. J. (1834) *Lond. med. surg. J.*, **6**, 321.
HERBST, R. H. (1928) *J. Amer. med. Ass.*, **91**, 1614.
MARION, G. (1933) *Congr. Soc. int. Urol.*, **5**, I, 392.
MERCIER, L. A. (1856) Recherches sur le traitement des maladies des organes urinaires. Paris.

Dr. G. S. Andrews: This paper presents the histological changes seen in the bladder neck biopsies removed from the 73 patients described by Mr. Mitchell in the preceding paper.

The biopsy fragments were small and the majority had been removed by diathermy which occasionally distorted the epithelial structures and part of the superficial epithelium was sometimes lost. This distorting effect was only superficial, however—its penetration being only a few millimetres—and the histological features to be described were quite clear.

Histological Changes

(1) *Squamous metaplasia.*—This was present usually in the urethra and less commonly in the urethral and prostatic glands and their ducts if they were present (Fig. 1). The degree of the metaplasia varied but it was usually very marked, although in some specimens many sections were searched before it was found.

(2) *Lymphocytic foci.*—Large collections of lymphocytes situated beneath the epithelium of the urethra were commonly seen; in some children these appeared almost large enough to have produced some narrowing of the meatus. In other specimens the lymphocytes were more diffusely arranged, being particularly prominent around the areas of metaplasia.

(3) *Œdema.*—It was commonly observed that the muscle bundles were widely separated by pale-staining connective tissue (Fig. 2). This was composed of delicate collagen fibrils separated by clear spaces in which no ground substance could be seen (Fig. 3). This appearance was thought to be due to œdema. It is similar to a change seen in the connective tissue of the prostate of the fœtus near term (Fig. 4) occurring at a time when the fœtal prostate usually shows massive squamous metaplasia.

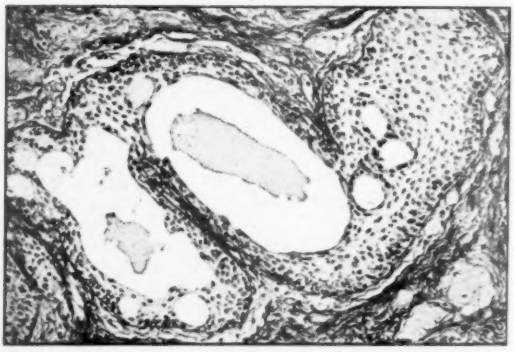


FIG. 1.—Squamous metaplasia in the ducts of the prostatic glands of a male aged 15 years. × 150.

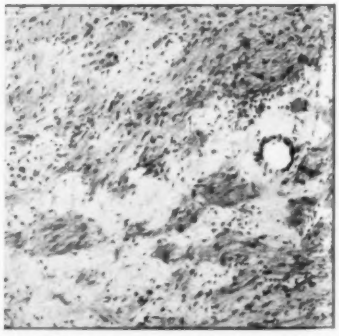


FIG. 2.–Œdematous connective tissue separating muscle bundles. Male aged 33 years. × 100.

(4) *Changes in the muscle fibres.*—These were seen best in transverse section of muscle bundles and appeared to be stages in a degenerative process. In the first stage the central cytoplasm of the fibre was pale and distinguishable from the normal staining periphery. Later the nucleus of the fibre was shrunken and pyknotic and the central cytoplasm disappeared leaving a perinuclear vacuole which eventually involved the whole cytoplasm (Fig. 5).

As the muscle fibres degenerated there was a thickening of connective tissue fibres both around the muscle bundle and also extending into it between its fibres. The final stage, in transverse section, was that of a wire-netting of collagen (Fig. 6).

Muscle bundles cut longitudinally appeared to be divided into short segments of normal and of vacuolated or fibrosed fibres.

Neither the cause nor the nature of this muscle degeneration could be determined. It varied in degree but as a general rule did not appear extensive enough to have produced serious interference with the muscle action.

(5) *Fibrosis.*—The amount of fibrous tissue normally present at the bladder neck varies and undoubtedly increases with age. However, in the present series, a significant increase in the amount of fibrous tissue was thought to be present in many specimens. This was particularly striking in the post-prostatectomy group (IV). In the others it appeared that the fibrosis was due to replacement of degenerate muscle fibres by collagen.

(6) *Muscle hypertrophy.*—It was estimated that muscle hypertrophy was present in some specimens

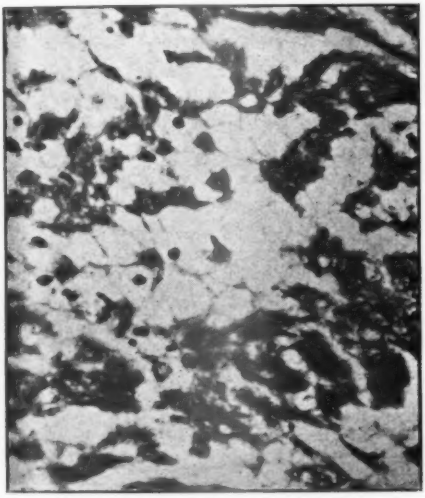


FIG. 3.—High-power view of œdematous connective tissue showing delicate collagen fibrils with no ground substance. Male aged 51 years. × 330.

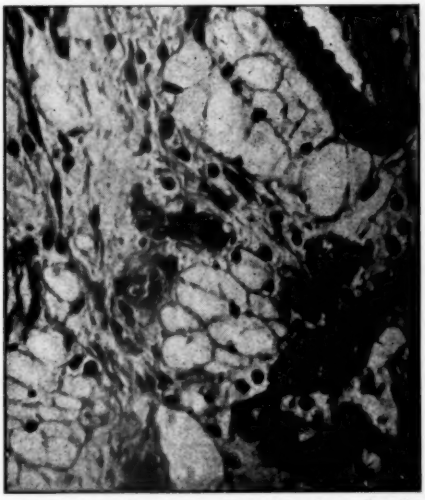


FIG. 4.—Œdematous connective tissue in the prostate of a full-term stillborn child for comparison with Fig. 3. × 330.

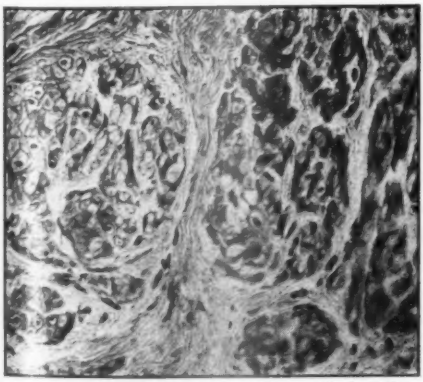


FIG. 5.—Transverse section of muscle bundles showing degeneration of fibres. The central cytoplasm of the fibres is pale staining and sometimes vacuolated. Male aged 15 years. × 250.

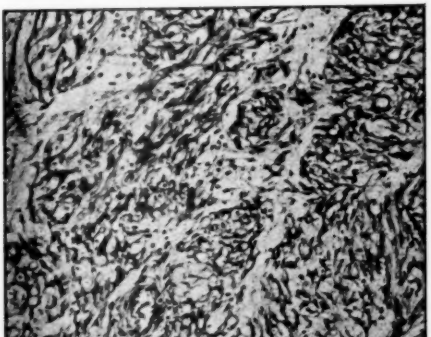


FIG. 6.—Transverse section of muscle bundles showing vacuolated fibres surrounded by collagen. Male aged 71 years. × 100.

but it was not a common finding. It was not found possible actually to measure the muscle fibres and to compare them with a series of normal controls, neither was it possible to state whether or not the hypertrophy occurred exclusively in the internal sphincter. It was thought that the hypertrophy was most probably secondary either to the obstruction or to the muscle degeneration.

(7) *Nodules.*—Small nodules or "adenomata" were present in 25 specimens. These were not usually at the bladder neck and had merely been included by the length of the biopsy strip. They were mainly of the stromal or fibromyomatous type. It was interesting that they did not occur exclusively in Group III which was the only group in which some enlargement of the prostate was noted clinically, and of the 6 cases in Group IV only 2 showed nodules, so that the recurrence of symptoms in this group was not due to a recurrence of benign hyperplasia.

Acute inflammation.—27 specimens were diffusely infiltrated with plasma cells (which predominated), eosinophils and neutrophil polymorphs. It was possible to show statistically that there was a significant correlation between the presence of acute inflammatory cells and a history of recent catheterization or other instrumentation.

Incidence of the histological changes.—This is shown in Table I. Despite the somewhat lower incidence in Group I, which is not remarkable in view of the smallness of some of the biopsies, there is

TABLE I.—INCIDENCE OF THE HISTOLOGICAL CHANGES IN THE WHOLE SERIES ARRANGED IN GROUPS

Group	Total	Squamous metaplasia	Lymphocytic infiltration	Œdematous connective tissue	Muscle degeneration	Fibrosis	"Adenoma"
I	16	9	11	12	9	8	0
IIA	22	19	18	22	20	14	5
IIB	16	15	16	12	16	12	7
III	13	12	11	11	12	9	11
IV	6	5	6	5	5	6	2
Total	73	60	62	62	62	49	25

no significant difference statistically between the groups. It is of particular interest that Groups IIA and IIB are similar since these groups are identical except that those patients in Group IIB gave a history of repeated urinary infections.

The variations in the degree of the changes within each group were similar. No correlation could be obtained between the degree of the changes and the age of the patient, the length of history or the clinical stage (*vide* previous paper, p. 549).

The small group of females showed the same changes as the males. In none of the specimens removed from females was there evidence of hyperplasia of the urethral glands so that the suggestion made by Folsom (1931) that a "female prostate" is the cause of the obstruction could not be substantiated.

Squamous metaplasia has not been described previously in these cases and its frequent occurrence in such small biopsy material, particularly that from the very young, increases its significance.

Squamous metaplasia sometimes occurs in the prostate, particularly in benign hyperplasia, and its incidence in the present series has been compared with that found in two series of prostates removed at post-mortem, the first being 142 prostates removed from males between the ages of 15 and 79 years and the second 19 prostates removed from children between the ages of 1 month and 15 years (Table II). Each prostate was examined histologically and no patient had complained of urinary obstruction.

TABLE II.—INCIDENCE OF SQUAMOUS METAPLASIA IN THE PRESENT SERIES COMPARED WITH THAT FOUND IN TWO SERIES OF POST-MORTEM PROSTATES

	Total	With squamous metaplasia	Without squamous metaplasia
Present series over 15 yrs. of age	58	52	6
142 post-mortem prostates 15–79 yrs.			
Normal	58	8	50
Benign hyperplasia	84	36	48
Present series under 15 yrs.	15	8	7
Post-mortem prostates 1/12–15 yrs.	19	0	19

Correlation between histological changes and cystoscopic appearance.—The changes were sometimes limited to or occurred maximally in the lateral or posterior segments of the bladder neck. This localization corresponded closely with the cystoscopic appearance of thickened lateral pillars or median bar. If the changes occurred in all parts of the bladder neck, the cystoscopic appearance was usually a thickened ring.

CONCLUSIONS

It is difficult to exclude entirely the possibility that the changes may be the result rather than the cause of the obstruction. However, the similarity between Groups IIA and IIB (Table I) excludes

chronic infection as an ætiological factor in the production of the histological changes. It is also important that there was no correlation between the degree of the changes and the length of history, for if the changes were the result of obstruction one would have expected them to be much more marked in those patients in whom the condition had existed for a long time.

Squamous metaplasia has been produced in the prostates of man and animals by the injection of œstrogens (Lisco and Biskind, 1941; Parkes and Zuckerman, 1935; Moore and McLellan, 1938; Nanson, 1950; Sharpey-Schafer and Zuckerman, 1941) and Zuckerman (1938) has observed large collections of lymphocytes beneath the urethral epithelium of monkeys receiving daily injections of œstrone. Lacassagne (1933) produced squamous metaplasia of the prostate with obstruction at the bladder neck in mice by giving œstrin.

The patients in the present series can be divided into two groups; those with a history of symptoms since birth and those presenting later in life at roughly the "prostate age". At both these times some degree of "hormonal imbalance" could reasonably be expected.

REFERENCES

Folsom, A. I. (1931) *J. Amer. med. Ass.*, **97**, 1345.
Lacassagne, A. (1933) *C. R. Soc. Biol., Paris*, **113**, 590.
Lisco, H., and Biskind, G. R. (1941) *Endocrinology*, **29**, 772.
Moore, R. A., and McLellan, A. M. (1938) *J. Urol.*, **40**, 641.
Nanson, E. M. (1950) *Brit. J. Urol.*, **22**, 394.
Parkes, A. S., and Zuckerman, S. (1935) *Lancet*, i, 925.
Sharpey-Schafer, E. P., and Zuckerman, S. (1941) *J. Endocrin.*, **2**, 431.
Zuckerman, S. (1938) *J. Anat., Lond.*, **72**, 264.

The Fate of the Bladder Neck and Prostatic Cavity after Prostatectomy

By Marco Caine, F.R.C.S.

Institute of Urology, London

I would like to present a few observations regarding the fates of the prostatic cavity and the region of the bladder neck following prostatectomy. These are features that have come to light during the examination of 519 patients, operated upon from one to five years previously at St. Peter's and St. Paul's Hospitals for benign prostatic obstruction.

The primary object of this investigation was an enquiry into the late results and sequelæ of the operations, and it is from this essentially clinical viewpoint that the following observations have been made.

Nearly fifty years ago Thomson Walker (1906), commenting upon the anatomical results of the Freyer type of prostatectomy, described the usual outcome as a posterior urethra destroyed down to the region of the verumontanum, with the prostatic cavity always full of urine: thus indicating a persisting incompetence of the bladder-neck sphincter. This picture of the wide open bladder neck has generally been accepted as the result to be expected in the normal course of events. However, as he pointed out even at that time, this is not inevitably the final outcome; for in some cases he found that the prostatic cavity was empty of urine both before and after micturition. Hence, he said, in these cases the bladder sphincter had regained its tone, and there was sufficient contractile power in the wall of the prostatic cavity to empty it completely of urine. It is this latter type of result, which Thomson Walker regarded as the exception, that I believe we may now hope to find in the most satisfactory type of case.

To deal first with the prostatic cavity itself: upon urethroscoping a patient with a satisfactory result, one sees a clean, healthy-looking region. The walls are free from crevices, and are mobile and elastic. The cavity is fusiform in shape, and its appearance approximates to that of a slightly dilated posterior urethra. In fact, in some instances it may be difficult to recognize endoscopically that a prostatectomy has been performed, although this is more obvious on a urethrogram owing to the greater distensibility of the prostatic cavity compared with the rest of the posterior urethra. Fig. 1 is a micturition urethrogram of such a case. In other cases, however, one sees a cavity with relatively rigid, grossly irregular walls like the inside of a severely trabeculated bladder, with large numbers of interstices between interlacing bands of tissue. They are frequently severely infected; and purulent debris and slough may persist in them years after operation. Such cavities show an impairment of their normal post-operative contraction, and are larger than one would expect from the size of the removed specimen. Between these two extremes are seen a large number of intermediate types, with varying degrees of irregularity, subinvolution and infection. (Illustrative urethrograms of such were shown.)

Such cavities may act as foci maintaining persistent, severe urinary infection long after prostatectomy. It is of importance, therefore, to elucidate the reasons for such unsatisfactory end-results.

The normal process of involution has been traced by Brodny and Robins (1950), and they have shown that this is a prolonged affair, taking many months to reach its final stage of epithelialization and full contraction.

What, then, are likely to be the factors interfering with this process, and preventing it following its normal course? In the first place, it should be noted that the size of the gland enucleated bears little relationship to the size of the ultimate cavity.

The type of operation performed does, however, appear to be of some significance, for it is found that these abnormalities are more commonly met with in those cases who have had operations employing suprapubic drainage of the bladder, than in the closed operations. The retropubic method is also, however, associated with poorly involuted and irregular cavities on occasions, particularly where there has been post-operative leakage of urine through the capsule, and associated sepsis. This is readily understandable, for the periprostatic fibrosis that must occur following such a leakage may well interfere with the normal contraction of the prostatic bed.

The operations employing suprapubic drainage have been accompanied, in many cases, by the use of packing or hæmostatic bags of one sort or another, and it is therefore difficult to dissociate these two factors from one another. However, packing was not used in all the cases, and it does not appear likely to be, *in itself*, the essential factor interfering with normal involution, for the packing is usually in place for only two to four days, whereas the contraction and repair of the prostatic cavity is, as already pointed out, a process which takes place over a prolonged period.

It seems probable that local infection is the prime cause, and its perpetuation the ultimate result of these abnormalities. Now, it is frequently observed that, on passing a urethral catheter on a patient with suprapubic drainage, who is recovering from a prostatectomy, a "sump" of almost pure pus is encountered. Much of this pus must lie within the prostatic cavity, and until urine is passed the natural way, will remain there as a stagnant pool. The presence of devitalized tissue, as may exist following excessive fulguration or the leaving behind of partially detached tags in the cavity, will favour this infection, and an irregular surface will provide recesses in which the pus will continue to lurk, even when urine is passed through the main cavity. The use of tight packing may have an *indirect* effect, both by acting as a foreign body promoting sepsis, and also by impeding free drainage from the prostatic bed and encouraging the infection to penetrate and establish itself in the deeper layers.

It is in the avoidance of these factors, then, that one may hope to prevent, or at any rate reduce, the incidence of such unsatisfactory cavities. The collection of a pool of pus in cases drained suprapubically is probably lessened by the use of a continuous irrigation. Careful visualization of the cavity during operation is essential; and if it is considered *necessary* to use packing, this should preferably be of a material that will not interfere with drainage, or encourage sepsis, as, for example, the Paul's tubing recommended by Winsbury-White.

There are two further types of prostatic cavities: The first group are those in which a definite lobule of prostatic tissue, or even a complete lobe, is found to persist or to have recurred. Although this tissue may not interfere with satisfactory emptying of the bladder, Flocks (1938) has shown that it may serve as a focus of persistent infection.

The other type is that in which excessive cicatrization has occurred, with the formation of a linear stricture.

There are clearly, in general terms, three fates that may befall the bladder neck. It may remain dilated and incompetent; it may return to a normally functioning, competent mechanism; or it may stenose and give rise to a post-prostatectomy bladder-neck obstruction. The first of these has long been regarded as the normal outcome of operation, and this is still so in many of the transvesical operations. The bladder neck *does* contract down to normal again on many occasions, however, and, as far as can be judged from the present series, this is more commonly seen after a retropubic or vesico-capsular operation, as would be expected, in view of the lesser trauma to the bladder neck involved in the sub-vesical operations: although the factor determining that the bladder neck should regain its tone and function has not been defined. Fig. 2 is an example of a satisfactory result of this nature. It is of the same patient as Fig. 1, taken after that picture, and after he had voluntarily ceased micturition. The prostatic fossa has contracted down and emptied, and the bladder neck closed firmly.

In contrast are Figs. 3 and 4, showing in the first an irregular prostatic cavity during micturition; and in the second, after stopping micturition, the open bladder neck, the prostatic cavity remaining filled, and the external sphincter acting as the controlling mechanism cutting off the flow of urine.

The third possible fate of the bladder neck involves post-prostatectomy bladder-neck obstruction, a not uncommon complication following operation. The most commonly used prophylactic measure is the excision of a wedge of tissue from the posterior aspect of the bladder neck and the trigone, but an alternative method, used in a lesser number of cases in this series, is a linear incision of the bladder neck in the posterior mid-line.

Despite such measures, however, the danger of obstruction developing has by no means been abolished. Wilhelm and Freed (1949) recorded its occurrence in 9 out of 33 retropubic prostatectomies, despite the routine excision of a wedge.

In the present series of cases, 65 patients developed a definite degree of stenosis or diaphragm formation at the bladder neck, so the evidence as to the efficacy of the two prophylactic measures used in this series was studied. As the question of excising or not excising a bladder-neck wedge, or of incising the bladder neck, could arise only in the various transabdominal operations, the transurethral pro-

cedures have been excluded also from the cases in which neither of these was done. Although they are not statistically conclusive, the relevant figures (Table I) lend support to the generally accepted belief

TABLE I

Bladder neck	Total No.	Number developing bladder-neck obstruction	%
Untouched	168	28	16·7
Wedge excised	238	27	11·3
Incised	26	5	19·2

that a wedge excision lessens the danger of bladder-neck obstruction developing, reducing its incidence from 16·7% to 11·3%, but by no means completely abolishes it. In contrast to this, the simple incision of the bladder neck actually appears to increase the tendency towards the development of obstruction at a later date.

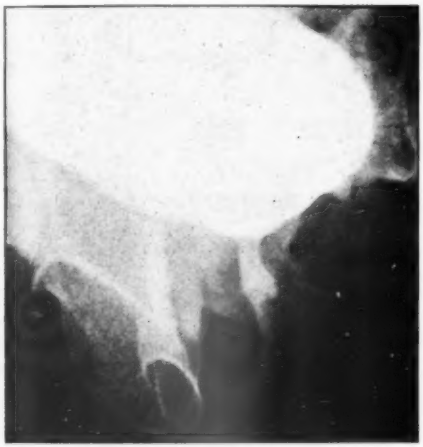


FIG. 1.—Well-contracted, fusiform, prostatic cavity three and a half years after retropubic prostatectomy. During micturition.

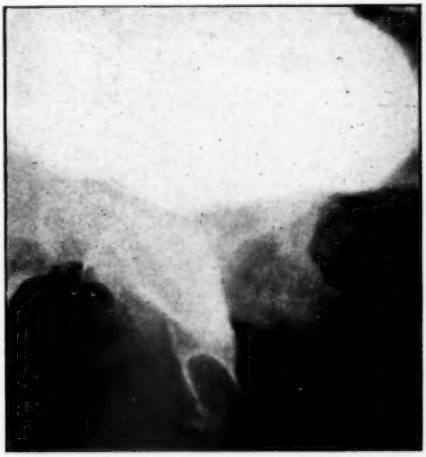


FIG. 2.—Same case as Fig. 1, on interrupting micturition. Note closure of bladder neck, and emptying of prostatic fossa.

FIG. 3.—Poorly contracted prostatic cavity, three and a half years after 2-stage Freyer prostatectomy. During micturition.

FIG. 4.—Same case as Fig. 3, on interrupting micturition. Note lack of closure of bladder neck, prostatic cavity still filled, and control of micturition by external sphincter only.

The failure of a wedge excision to eradicate this complication may be dependent to some extent upon the shape of the wedge. If this takes the form of a deep, relatively narrow "V" it is reasonable to conceive that after the operation, when the parts are at rest, the two edges of the "V" may easily fall together and cross-union occur. The subsequent fibrosis and contraction will then, in a certain proportion of cases, give rise to constriction, or even diaphragm formation, at the bladder neck. In the case of a simple incision, which may appear to afford a smooth path from the prostatic cavity into the bladder when spread out at operation, the likelihood of the edges falling together again in the post-operative period is very much greater, and the subsequent healing and fibrosis will then cause more constriction of the bladder outlet than if it had not been touched at all.

A consideration of the effectiveness of these two procedures in relationship to the type of prostate dealt with gives the result shown in Table II. Many of the groups are reduced to such small dimensions by this degree of subdivision that strict statistical comparisons cannot be drawn. Nevertheless,

TABLE II

Type of prostate	Bladder neck	Total No.	Number developing bladder-neck obstruction	%
Adenomatous..	Untouched	164	27	16·5
	Wedge excised	197	25	12·7
	Incised	15	5	33·3
Fibrous	Untouched	4	1	(25)
	Wedge excised	22	0	—
	Incised	5	0	—
Muscular and fibromuscular	Untouched	0	0	—
	Wedge excised	19	2	10·5
	Incised	6	0	—

it does appear from these figures that a wedge excision of the bladder neck is more effective in preventing this sequela in the fibrous group than in the adenomatous prostates. This may well be a reflection of the much greater rigidity of the bladder neck in the fibrous cases, and hence the greater likelihood of the "V" remaining open in the immediate post-operative period.

It would seem essential, therefore, that any attack upon the bladder neck, if it is to be effective, must be fashioned in such a manner as to obviate the possibility of raw surfaces coming together and uniting. A broad, relatively shallow wedge is much more likely to fulfil this requirement than is the deep narrow type, and it is probable that the use of this type of wedge in many cases has produced such benefit as is reflected in the figures referred to above.

Other methods of prevention should be investigated such as the Block Excision suggested by Harris (1935) which, although originally designed for the treatment of "Maladie du Col", would seem equally applicable to the bladder neck after enucleation of an enlarged prostate, or the procedure of bilateral internal sphincterotomy recently suggested by Wells (1952).

The problem of post-prostatectomy bladder-neck obstruction requires further critical work before the final solution can be reached.

SUMMARY

Reference has been made to what may be regarded as the ideal fate of the prostatic cavity and bladder neck after prostatectomy, but this ideal is not always attained. An attempt has been made to elucidate some of the factors associated with the imperfect results, and some suggestions regarding their avoidance made.

This work has been carried out under the ægis of the Institute of Urology. My thanks are due to the Surgeons at St. Peter's and St. Paul's Hospitals, for their kind help.

REFERENCES

BRODNY, M. L., and ROBINS, S. A. (1950) *J. int. Coll. Surg.*, **14**, 143.
FLOCKS, R. H. (1938) *J. Urol.*, **40**, 208.
HARRIS, S. H. (1935) *Brit. J. Surg.*, **23**, 45.
WALKER, J. T. (1906) *J. Anat., Lond.*, **40**, 189.
WELLS, C. (1952) Prostatectomy, a Method and its Management. Edinburgh.
WILHELM, S. F., and FREED, S. Z. (1949) *J. Urol.*, **62**, 660.

Bladder-neck Obstruction in Women [*Abridged*]

By THOMAS MOORE, M.D., M.S., F.R.C.S.

Manchester

ALL degrees of urinary obstruction due to changes at the bladder neck occur in women. Since Caulk (1921) reported the first case over 100 have appeared in the American literature: Folsom (1931), Nesbit (1933), Fite (1934), Caulk (1937), Thompson (1939), Young (1940), Mirabile (1943), O'Connor (1945), Jacobson (1946) and Emmett *et al.* (1950). Very few have been reported in Britain: Van

Houtum (1935) 6 cases, Winsbury-White (1936) 2 cases, Coutts and Vargas-Zalazar (1945) 3 cases, and Mills (1952) 3 cases. During the last four years I have encountered 11 cases. Transurethral resection of the bladder neck with the Thompson cold punch has proved the treatment *par excellence.*

Ætiology and pathology.—Histological examination of tissue removed has shown glandular hyperplasia, inflammatory infiltration and fibrosis or muscular hypertrophy. Folsom (1931) and Young (1940) have been impressed by the glandular hyperplasia which was so great that the tissue histologically resembled that removed from the bladder neck in the male. Folsom (1931), Folsom and O'Brien (1945), Johnson (1922), Young (1940), Lintgen and Herbut (1946) believe that glands are normally present in the female urethra and are the homologue of the prostate in the male. Experimentally and clinically hyperplasia of these glands can be caused by hormonal stimulation. Young (1940) has published a case of adrenal virilism in which this was so extreme that the urethra was surrounded by a structure which resembled the prostate. Thompson (1939), Emmett and MacDonald (1942), and Emmett *et al.* (1950) maintain that no glands are present in the female urethra and the gland-like structures sometimes seen are derived from Brunn's nests. In my cases, true glandular hyperplasia has not been found. In one, gland-like cavities lined by flattened and columnar epithelium were present (Figs. 1 and 2), but these were probably not derived from urethral glands. The changes commonly found have been squamous metaplasia of the epithelium, œdema of the tunica propria and infiltration with inflammatory cells (Fig. 3). Occasionally, inflammatory changes extend into the muscular coat (Fig. 4). In one case, some hypertrophy of the urethral muscle was present (Fig. 5) (Thompson, 1939).

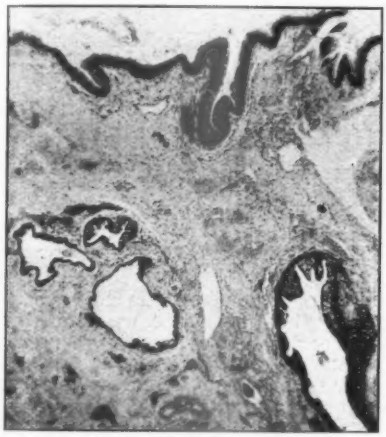


FIG. 1.—Gland-like spaces. × 22.

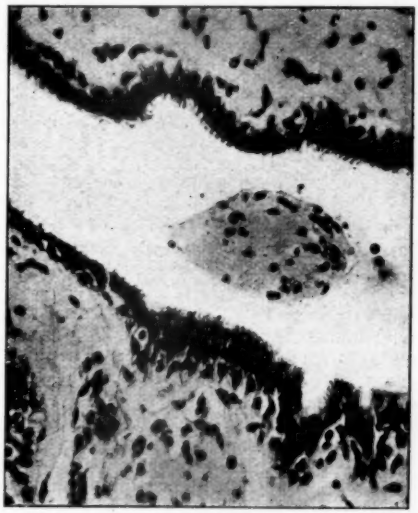


FIG. 2.—Columnar epithelium lining. × 300.

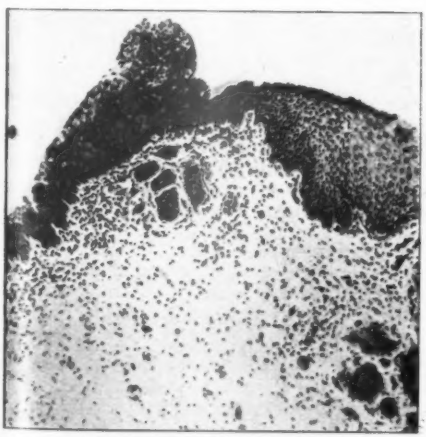


FIG. 3.—Inflammatory change in the submucosa and squamous metaplasia of the epithelium. × 90.

The changes at the bladder neck, although often minimal, cause urinary obstruction with the usual sequence of bladder hypertrophy, residual urine (R.U.), upper urinary tract dilatation and dysfunction. The bulk of new tissue is never sufficient to cause mechanical obstruction. One must presume that the normal opening of the bladder neck is disturbed. Except in those cases in which inflammatory changes are present in the muscle itself the mechanism of this dysfunction is difficult to understand.

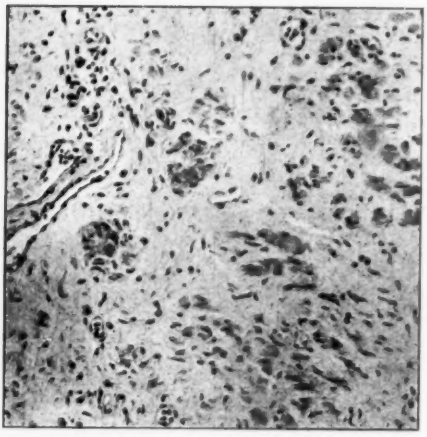


FIG. 4.—Infiltration of muscle with fibrous tissue. × 130.

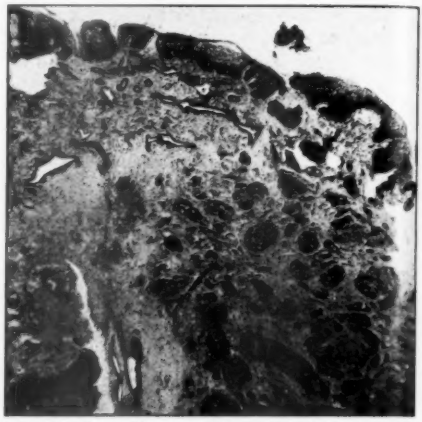


FIG. 5.—A small part of the muscle hypertrophy. (Case 5.) × 25.

Possibly the primary lesion is sometimes a neuromuscular inco-ordination of the bladder neck (Case 5). The inflammatory changes found could be secondary. As the cervix is usually healthy—the condition is quite common in elderly spinsters—the infection must ascend along the urethra.

Clinical features.—Although any age group may be affected, the condition occurs most commonly after 50 years of age. Acute or chronic retention of urine may be present. Most of the reported cases have been of this type. I believe that many cases are missed because true obstructive symptoms are not marked. Frequency of micturition, dysuria and hæmaturia—symptoms due to the secondary effects of the incomplete bladder emptying—may be prominent. In some cases the symptoms are those of uræmia (Case 10). On clinical grounds my cases can be grouped as follows:

Group I: Urinary difficulty with small or moderate amounts of residual urine (1 case).
Group II: Acute retention (2 cases).
Group III: Chronic retention (2 cases).
Group IV: Cystitis (3 cases).
Group V: Hæmaturia (1 case).
Group VI: Uræmia (1 case).
Group VII: Enuresis (1 case).

Diagnosis.—The presence of urinary obstruction is sometimes very obvious (Groups II and III). More often it must be demonstrated by more detailed investigation. The estimation of the residual urine by bimanual examination after micturition, catheterization and intravenous urography (I.V.U.) is essential. The presence of urinary infection and renal dysfunction must be sought by the usual methods. Cystoscopy is the most important procedure. Trabeculation demands careful study of the bladder neck but in cases with minimal obstruction and of recent onset it may be absent. The mucosa at the bladder neck may be œdematous, swollen and the site of inflammatory polypi. In long-standing cases it might be white, thickened or rigid. With either the right-angle or fore-oblique lens a definite elevation of the posterior quadrant forming a bar obstruction can be seen. Sometimes, swelling of the postero-lateral quadrants may simulate prostatic lobes. Sometimes there is circumferential thickening suggesting hypertrophy of the sphincter. In no case have I been able to appreciate any thickening on palpation of the bladder neck either against the pubis or the cystoscope. On one occasion the changes seen suggested carcinoma, and this was subsequently confirmed (Case 8).

Differential diagnosis.—Mechanical causes of urethral obstruction: (1) From above: Ureterocele and pedunculated neoplasms in the bladder and any other cause of mechanical obstruction of the urethra from above are easily excluded by cystoscopy.

(2) External pressure: Conditions causing pressure on the urethra, e.g. cervical fibroid, are easily excluded by careful vaginal or rectal examination.

(3) Narrowing of the urethra: Stricture of the urethra, simple or malignant, can cause no difficulty in diagnosis. It is easily excluded by careful palpation and sounding.

Neurogenic bladder: Dysfunction of the bladder due to disease of the nervous system can only be excluded by the absence of other signs of nervous disease and by the presence of the definite endoscopic findings at the bladder neck. One of my patients suffered from diabetes and although there was no other clinical sign of a lesion of the nervous system, the cerebrospinal fluid protein content was raised

to 110 mg. per 100 c.c. and it is just possible that the bladder dysfunction was the first evidence of a diabetic neuropathy (Lich and Grant, 1948; Kutzman, 1948). There were, however, definite signs of obstruction at the bladder neck.

Hysteria: This is the condition most difficult to exclude. I do not deny that it is sometimes the cause of urinary difficulty but believe that many of these patients are really suffering from bladder-neck obstruction. This is confirmed by the trabeculated bladder and definite obstructive changes at the bladder neck. When such changes are present, transurethral resection (T.U.R.) can be recommended with confidence (Case 11).

Post-operative retention of urine in women.—Males with some prostatic obstruction often develop urinary retention after any operation; I have suggested (Moore, 1952) that both the prostate and the primary disease should, where possible, be treated at the same time. However, when a female develops post-operative retention of urine the condition is generally regarded as being hysterical. Apart from those cases in which operation directly interferes with the urethra, e.g. colporrhaphy, or is in such a place that straining at micturition causes pain so that reflex retention of urine might occur, I have no doubt that many are due to pre-existing bladder-neck obstruction. As in the male, when the bladder is allowed to distend after operation, complete retention occurs.

Relationship of bladder-neck obstruction to cystocele.—In my opinion cystocele rarely, if ever, causes urinary obstruction *per se*. The bladder has its own power of contraction and should not be affected by any loss of external support. When any urinary difficulty exists in cases of cystocele it is most likely due to unassociated changes at the bladder neck. If this is not recognized and treated, operative repair of the cystocele is almost certain to fail (Case 1).

Treatment.—When the degree of obstruction is sufficient to cause severe renal dysfunction, pre-operative treatment by an indwelling catheter may be necessary. In severely infected cases also, a few days' treatment with antibiotics and catheter drainage will make operation much safer. The obstruction should be removed transurethrally. I always use a Thompson punch. This must be used with even more care in the female than in the male because the sphincter is more easily damaged and the bladder neck more easily perforated. The shaft should be held just outside the external meatus between the thumb and the middle finger of the supinated left hand. The index finger must be held against the anterior vaginal wall all the time, so that the depth and extent of the cutting can be felt. The cutting window of the instrument, which is 2 cm. long, should never be more than half open. Small bites of tissue are removed all round the bladder neck but particularly from the posterior and postero-lateral quadrants. The amount varies from 1–2 grammes. It is astonishing in some cases how little has to be done to cause great improvement in the symptoms. Even in cases in which cystoscopically it might be difficult to convince oneself that an obstruction is present, it is always worth while trying the effect of a transurethral resection. In my cases, more than one resection has not been necessary for cure, but one should not hesitate to repeat the procedure if the residual urine is not eliminated by the first treatment.

Post-operative complications.—(1) *Vesico-vaginal fistula:* This may occur at operation due to cutting too deeply, or, later, from the use of too much diathermy in securing hæmostasis. Both may be avoided by careful technique.

(2) *Incontinence of urine:* This is due to cutting too distally in the urethra and is avoided by the technique described.

The only other complications are associated with urinary infection, which is usually present before operation. A satisfactory resection combined with the necessary antibiotics is the best way of overcoming this.

Results.—In all cases symptoms have been relieved and the residual urine reduced to less than 2 oz. One patient aged 75 years succumbed some little time after operation from ascending pyelonephritis.

Case Histories

Group I

Case 1.—E. S., aged 45. Married. 4 children.

Seen September 1952. Frequency and difficulty for many years. Failed colporrhaphy 1940, 1946 and 1947.

On examination.—General condition: good. Large cystocele present. R.U. 4 oz. No urinary infection. I.V.U. normal. Blood urea 28 mg.%.

Cystoscopy: Marked trabeculation of the bladder. Definite bar posteriorly at the bladder neck. T.U.R. *Histology:* Fibrosis of the submucosa and considerable fibrosis of the muscle tissue. *Result:* Symptoms entirely relieved by the operation. No R.U. (The patient stated "It is heaven to pass water like this".)

Group II

Case 2.—E. S., aged 74. Unmarried.

Seen October 1948. Acute retention of urine for one week. Catheterized twice daily at home.

On examination.—General condition good. Bladder distended nearly to the umbilicus. Other systems: N.A.D. Urine: W.B.C. +++. Culture: *B. coli.* Blood urea 35 mg.%. Hb 68%. R.B.C. 3,700,000 per c.mm. *Cystoscopy:* Trabeculated bladder. Definite elevation of the posterior quadrant of the vesical neck.

T.U.R. *Histology:* Squamous metaplasia of the epithelium and diffuse inflammatory change in the tunica propria. *Result* excellent. R.U. reduced to less than 1 oz.

Case 3.—E. C., aged 59. Married.

Seen November 1952. Had suffered from diabetes for many years. Acute retention of urine after operation on right cataract. Catheterized twice daily for ten days. Urine sterile. I.V.U. normal. *Cystoscopy:* Definite trabeculation of the bladder with bar at the bladder neck. After this, bladder function improved. January 1953 patient symptom-free. R.U. 5 oz. As the patient was in such poor general condition and was symptom-free, it was not considered that T.U.R. was justified.

Group III

Case 4.—A. M. S., aged 75. Unmarried.

Seen September 1950. Nocturnal incontinence for twelve months.

On examination.—General condition poor. Bladder distended to the umbilicus. Other systems: N.A.D. Urine: W.B.C. +++. Culture: *B. coli.* Blood urea 28 mg.%. Hb 84%. I.V.U. normal. *Cystoscopy:* Very trabeculated bladder. Marked œdema round the bladder neck with a bar posteriorly.

T.U.R. Vesico-vaginal fistula was caused during this operation and was repaired. *Histology:* Fibrous mucosa and infiltration with inflammatory cells. *Result:* Patient passed urine normally afterwards but gross urinary infection was present. Died three months later from ascending pyelonephritis.

Case 5.—E. E., aged 49. Married. 4 children.

Seen August 1951. Frequency of micturition for three weeks. Catheterized at irregular intervals at home.

On examination.—General condition good. Bladder distended to the umbilicus. Vaginal examination normal. *C.N.S.* (Dr. Fergus Ferguson): Patient always thought and spoke slowly. Pupil and tendon reflexes were also slow but no abnormality found. Urine sterile. I.V.U. normal. Hb 60%. R.B.C. 5,000,000 per c.mm. Blood urea 26 mg.%. W.R. negative. *Cystoscopy:* No trabeculation of the bladder. Definite elevation of the posterior quadrant and posterior parts of the lateral quadrants.

T.U.R. *Histology:* Marked squamous metaplasia of the epithelium with some infiltration of inflammatory cells. Considerable hypertrophy of muscle present. *Result:* The patient passed urine very well afterwards and the R.U. gradually fell to less than 2 oz. No recurrence. In this case it is believed that the primary cause was an inco-ordination at the bladder neck as there seemed to be a general slowness of all her nervous reactions.

Group IV

Case 6.—E. S., aged 76. Married.

First seen September 1951. Scalding on micturition for years. Acute retention seven years ago relieved by catheter drainage. Cystoscopy then said to be normal.

On examination.—General condition poor. Abdomen normal. Other systems normal. Urine: W.B.C. ++. Culture *B. coli.* Blood urea 83 mg.%. Hb 60%. R.B.C. 4,800,000 per c.mm. R.U. 26 oz. *Cystoscopy:* Bladder very trabeculated. Thickening all round the bladder neck.

T.U.R. *Histology:* Inflammatory infiltration of the submucosa. Much squamous metaplasia of the epithelium. Infiltration of muscle with hyaline fibrous tissue. *Result* excellent. Patient afterwards passed urine normally. R.U. less than ½ oz. No recurrence.

Case 7.—M. M., aged 78. Married.

Seen September 1951. Cystitis for two years.

On examination.—General condition good. Bladder palpable just above the pubis. No other abnormality on clinical examination. I.V.U. normal. Blood urea: 30 mg.%. Hb 78%. R.B.C. 3,900,000, per c.mm. Urine: W.B.C. +++. Culture *B. coli. Cystoscopy:* No trabeculation of the bladder. Slight elevation of the posterior quadrant of the bladder neck. Some inflammatory swelling of the lateral quadrants of the bladder neck. T.U.R. refused. Urinary infection overcome with antibiotics. Patient still living a normal life and bladder still distended up to the umbilicus. Urinary infection kept under control by occasional courses of antibiotics. There has been no deterioration of renal function.

Case 8.—C. K., aged 66. Married.

Seen September 1949. Frequency of micturition for three and a half years. Seen by a gynæcologist who carried out colporrhaphy three years ago. (It is a source of astonishment to me why women with urinary symptoms are so frequently referred in the first place to gynæcologists.) Afterwards a urologist found urethral stricture with secondary cystitis and treated the patient by regular urethral dilatation.

On examination.—General condition fair. Abdomen normal. P.V. normal. Urethra normal. No other abnormality found on clinical examination. Urine: W.B.C. +++. Culture: *B. coli.* I.V.U. normal. *Cystoscopy:* Urethra very narrow. Dilated before cystoscope could be passed. Bladder showed general inflammatory change. There was a hard ridge at the bladder neck posteriorly with considerable polypoid swelling of the mucosa over it which appeared to bleed very easily. It was suspected that the condition was malignant. Patient had a course of Aureomycin and symptoms were gradually relieved. Two months later, R.U. 4 oz. Urinary difficulty persisted although urine sterile.

T.U.R. *Histology:* Infiltrating transitional-cell carcinoma of the bladder. Symptoms persisted. Patient's life was very miserable and radical surgery decided upon. January 1950 to confirm diagnosis—bladder opened suprapubically. Normal apart from some cartilaginous-like infiltration at the posterior margin of the bladder neck such as might easily have followed previous T.U.R. with secondary infection. Large portion removed for histological examination. Bladder closed. Bilateral uretero-sigmoidostomy carried out. *Progress:* Patient very well after operation and entirely relieved of her symptoms. Biopsy confirmed the presence of carcinoma of the bladder neck. Radiotherapist advised against any type of local irradiation. Patient lived quite a normal life for eighteen months. Neoplasm eventually ulcerated through the vagina. No treatment given and patient died within a few weeks from hæmorrhage without suffering any further pain.

Group V

Case 9.—E. K., aged 59. Married.

Seen March 1952. Hæmaturia for seven days. Urinary difficulty for many years.

On examination.—General condition good. Bladder not distended. No other abnormality on clinical examination. Urine: W.B.C. ++. Culture: *B. coli.* I.V.U. normal. R.U. 1 oz. *Cystoscopy:* Marked trabeculation of the bladder. Definite posterior bar at the bladder neck.

T.U.R. *Histology:* Marked œdema of the submucosa with inflammatory infiltration extending into the underlying muscle. *Result* excellent. No R.U. All symptoms relieved. No recurrence to date.

Group VI

Case 10.—J. A. C., aged 63. Married.

Seen September 1951. Vomiting and diarrhœa for seven days. Urinary difficulty for some months.

On examination.—Very ill. Bladder distended to the umbilicus. Other systems normal. Urine R.B.C. and W.B.C. ++; sterile. Blood urea 157 mg.%. Hb 44%. Continuous catheter drainage for seven days. Blood urea fell to 22 mg.%. *Cystoscopy:* Bladder very trabeculated. Definite elevation of the posterior quadrant of the bladder neck with considerable inflammatory swelling of the mucosa.

T.U.R. *Histology:* Marked squamous metaplasia. Some gland-like structures present in the submucosa, some lined by columnar epithelium. Several Brunn's nests present. Much muscle tissue. *Result:* Patient passed urine normally afterwards. R.U. 1 oz. No recurrence of symptoms to date.

Group VII

Case 11.—A. B., aged 20. Unmarried.

Seen September 1952. Complained of bed-wetting on and off since birth. She did not have the normal desire for micturition and found urination slow and difficult. Previously seen by several psychiatrists and regarded as hysterical.

On examination.—General condition good. Patient appeared to be definitely "neurotic" and had several hysterical attacks while in hospital. Abdomen normal. C.N.S. normal. Urine: W.B.C. +++. Culture: *B. coli.* I.V.U. normal. Blood urea 25 mg.%. R.U. 10 oz. Hb 98%. Cystometry: Hypotonic type of curve. *Cystoscopy:* Very trabeculated bladder. Definite elevation of the posterior quadrant of the bladder neck with œdema of the submucosa.

T.U.R. *Histology:* Marked squamous metaplasia of the epithelium. Considerable inflammatory œdema of the submucosa. *Result* excellent. R.U. less than 1 oz. No further enuresis or difficulty on micturition. No recurrence to date.

This case shows how careful one must be before deciding that any condition is primarily functional in origin. No doubt anyone having organic difficulty with micturition for many years, for which no adequate treatment had been given, would become "neurotic".

It is a pleasure to record my indebtedness to Professor A. Colin Campbell, Professor of Pathology at the University of Manchester, for his help.

REFERENCES

CAULK, J. R. (1921) *J. Urol.*, **6**, 341.

—— (1937) *Int. Clin.*, **4**, 136.

COUTTS, W. E., and VARGAS-ZALAZAR, R. (1945) *Brit. J. Urol.*, **17**, 136.

EMMETT, J. L., HUTCHINS, S. P. R., and MACDONALD, J. R. (1950) *J. Urol.*, **63**, 1031.

——, and MACDONALD, J. R. (1942) *J. Urol.*, **48**, 257.

FITE, E. H. (1934) *Urol. cutan. Rev.*, **38**, 163.

FOLSOM, A. I. (1931) *J. Amer. med. Ass.*, **97**, 1345.

——, and O'BRIEN, H. A. (1945) *J. Amer. med. Ass.*, **128**, 408.

JACOBSON, C. E. (1946) *New Engl. J. Med.*, **235**, 645.

JOHNSON, F. P. (1922) *J. Urol.*, **8**, 13.

KUTZMAN, N. (1948) *J. Urol.*, **59**, 872.

LICH, R., and GRANT, O. (1948) *J. Urol.*, **59**, 863.

LINTGEN, C., and HERBUT, P. A. (1946) *J. Urol.*, **55**, 298.

MILLS, W. G. Q. (1952) *Brit. J. Urol.*, **24**, 236.

MOORE, T. (1952) *Brit. med. J.*, i, 362.

MIRABILE, C. (1943) *New Engl. J. Med.*, **228**, 751.

NESBIT, R. M. (1933) *Urol. cutan. Rev.*, **37**, 291.

O'CONOR, V. J. (1945) *J. Amer. med. Ass.*, **128**, 412.

THOMPSON, G. J. (1939) *J. Urol.*, **41**, 349.

VAN HOUTUM, G. (1935) *Proc. R. Soc. Med.*, **28**, 1511.

WINSBURY-WHITE, H. P. (1936) *Lancet*, i, 1008.

YOUNG, H. H. (1940) *J. Amer. med. Ass.*, **115**, 2133.

Mr. H. P. Winsbury-White said he thought fibrous obstruction was very common. When he found more than 8 oz. of urine retained he opened the bladder and resected the bladder neck suprapubically. This gave him the opportunity of feeling the fibrosis, and he was impressed with the commonness of its occurrence.

With the lesser cases the speaker carried out a transurethral resection, but it was easy to see the adenomatous tissue and to recognize it. His finding in all these cases, compared with adenomatous obstruction, was that 40% of bladder-neck obstructions were of a fibrous nature.

It was very important to treat this trouble at the beginning. He always urethroscoped children with disturbances of micturition. One could then see the granulomatous conditions and the seeds of the disease being sown in early childhood. There was an inflammatory process which, no doubt, continued.

Mr. Caine had mentioned suprapubic draining in prostatectomy; it had to be remembered that these could be very bad cases of chronic prostatitis. He examined several cases which he thought to be carcinoma for which he did a permanent suprapubic cystostomy. The result of the bladder drainage for several months in each case was that the prostate became quite soft. When a pre-operative examination of a prostate was made, areas of thickening—a chronic inflammatory process—were often noticed. This contributed very much to post-operative trouble. In women Mr. Winsbury-White did not like the transurethral resection, but performed a suprapubic resection instead. He was at the same time conscious of the danger of incontinence from suprapubic resection and of causing a vesico-vaginal fistula by the suprapubic route. This latter danger could be avoided by keeping one finger in the vagina during the resection.

Mr. Alex Roche said that he personally used the suprapubic approach as avoiding the perurethral risk of vesico-vaginal fistula. He opened the bladder and removed all the firm tissue at the bladder neck. He remembered four or five cases in the last few years, with a long history and huge residual urine, the removed tissue being microscopically fibrous, œdematous, and so on. The residual urine decreased, but these bladders, lying in floppy redundant fibrous-looking folds, probably had a fibrotic anatomy and could not fully contract again so as to abolish the residual urine.

Was one justified in resecting apparently redundant parts of the bladder, in addition to the fibrous tissue at its neck?

Professor Charles Wells said that he had carried out a number of resections of the posterior margin of the obstructed bladder neck. He had found on a number of occasions that the removal of a piece of tissue in the mid-line was followed by a recurrence of obstruction, owing to the falling together and subsequent fusion of the sides of the gutter. A further similar resection might be followed by a further relapse due to similar causes and every time a piece of tissue was removed the circumference of the internal meatus become smaller! It seemed, therefore, logical to attempt to increase the size of the opening without removing any tissue.

Latterly he had been making a little horizontal cut to the right at three o'clock and to the left at nine o'clock, without removing any tissue. The downward and backward pull of the trigone opens out the two incisions and the medial tissue falls back. There is no tendency for the sides of the cuts to fall together. There is no loss of tissue from actual removal and the small wounds have a good chance of epithelializing in the open position.

Professor Wells then showed films of a woman of 48. She had had three children of whom the youngest was 3½ and it was evident that the whole of her urinary disability had developed since the birth of the last child. The first interesting point, therefore, was that this was an example of acquired bladder-neck obstruction in a woman. The speaker thought this was a not unusual occurrence in women. When seen, the bladder was dilated to the size of a twenty weeks' pregnancy, but there was no demonstrable function in the right kidney, and an enormous hydronephrosis on the left. After other methods had failed, a minimal transurethral resection was carried out at three o'clock and nine o'clock. Back pressure was relieved and several months later the right kidney was removed because it was grossly infected. Two years after the operation the X-ray showed a normally emptying bladder and a satisfactory pyelogram on the remaining left side. Cultures of the urine proved sterile. These later pictures illustrated the efficacy of the method of resection, the power of recovery of the hydronephrotic kidney, and the possibility of sterilizing the urinary tract once the blockage has been removed.

Mr. David Band agreed with Mr. Moore when he said that a complete urological examination of the female was very often neglected. Not long ago he saw an unmarried woman in her forties who had had some difficulty with her bladder with frequency of micturition. She had been seen elsewhere and had not been completely examined. The endoscopic examination was equivocal. Fortunately, he examined her under anæsthesia, and through the vagina one could palpate a little mass just behind the bladder neck. A biopsy was made both from the vaginal and urethral aspects and an unsuspected carcinoma of the bladder neck was found. In this case there was a high degree of malignancy and a grave problem in surgery was presented.

The President said that the number of children suffering from this condition seemed considerable but it was doubtful if it would justify a very extensive use of a child's resectotome.

In infection of the post-prostatectomy cavity he had found that an extensive infected renal residual urine might sometimes be the source.

With regard to bladder-neck obstruction in women Mr. Roche's suggestion of the fibrous atonic bladder might explain some occasional failure of transurethral resection. (Some cases were hysterical and he usually quoted the patient who passed water only once a day. But after cystoscopy on St. Swithin's day she had been incontinent ever since.)

He had not tried removing a portion of a very large bladder and thought that, as the atony was mainly due to lack of muscle, it was unlikely such a resection would be successful.

Section of Medicine

President—Sir ALUN ROWLANDS, K.B.E., M.D., F.R.C.P.

[*February* 24, 1953]

DISCUSSION ON THE DIAGNOSIS AND TREATMENT OF ADDISON'S DISEASE

Professor D. M. Dunlop[1] said that since 1930 he had looked after 62 cases of Addison's disease. In 36 of these the ætiology was probably tuberculous; 2 showed malignant destruction of the suprarenals at autopsy; and one, still alive, gave positive serological tests for syphilis—a possibly fortuitous association. Males and females appeared in the series in practically equal numbers. All but 5 of the patients were between 20 and 50 years of age when first seen. The youngest was 14 and the oldest 56.

The clinical features of the disorder as they occurred in the series were then described. Feelings of tiredness and weakness were invariable symptoms and a greater or less degree of weight loss was always noted. Some unusual pigmentation of the skin was found in all but one patient. The pigmentation was illustrated by numerous colour photographs and its ætiology discussed. The highest blood pressure recorded in an untreated case was 120/90 in a middle-aged patient who had been hypertensive before developing Addison's disease. Two-thirds of the patients had systolic pressures between 90 and 110 and diastolic pressures between 60 and 70. Anorexia and nausea occurred in 80% of the patients. Abdominal pain was an ominous symptom usually heralding the onset of crisis. Most of the untreated patients were hypoglycæmic in the early morning making them difficult to arouse from sleep. 30% reacted violently to the insulin they secreted in response to a high carbohydrate meal.

70% of the patients conformed to the classical pattern outlined and presented little diagnostic difficulty. The only non-clinical diagnostic investigation which was really necessary in these was the routine X-ray of the chest and abdomen. In the remainder the diagnosis depended on the discriminating use of a number of tests, none of which alone could give a definite answer apart from the radiological demonstration of adrenal calcification. Comparison of the volume of day and night urine; the Robinson-Power-Kepler test; the estimation of the urinary 17-keto-steroids; and the insulin sensitivity test had all proved of value in his hands. His experience of the Thorn test was limited but several equivocal results had been obtained.

The story of prognosis in Addison's disease fell into four easily defined eras. The first lasted from 1849, when the disease was recognized as a clinical entity, till 1930. During this time all attempts at treatment were in vain and the great majority of sufferers died within two years of the onset of the malady. In 1930 a potent cortical extract prepared by Swingle and Pfiffner was introduced and with the emphasis which Loeb placed on the value of salt in treatment the period 1930–1939 could be called the era of cortical extract and salt. The third era was that of deoxycortone acetate synthesized by Steiger and Reichstein in 1937 which became generally available for injection and implantation in 1939. The years 1939–1951 could be called the DCA era. It was apparent during the last two years when cortisone had become more freely available that a fourth, or cortisone and DCA, era had dawned.

Between 1930 and 1938 30 patients were treated and the results showed little improvement over the first era in spite of salt and cortical extract. 23 patients died within a year of diagnosis, 2 within two years and 2 within three years. Only 2 survived into the third era. 30 patients were treated in the 1939–1951 or DCA era and the results were definitely better. 14 lived into the fourth era; 16 were dead by 1951. Counting up all those, alive or dead, who had lived longer than two years the total was 15 compared with only 4 in the previous era. Counting up those who had lived longer than 5 years, there were 9 in the 1939-1951 series, whereas no case had attained that life-span previously. A greater knowledge of the use of cortical extract and intravenous fluid in crisis, and a more careful and regular supervision of the patients contributed to the improved results obtained by DCA.

[1]Summary of Professor D. M. Dunlop's opening paper on the Diagnosis and Prognosis of Addison's Disease based on work from his department published previously (Kinnear, T. W. G., Rolland, C. F., Matthews, J. D. (1952) *Edinb. med. J., Trans. med-chir. Soc.*, Session CXXXI, p. 63).

All 14 patients surviving into the fourth era and 2 new ones were still alive. There had been no deaths in the last two years. One patient had now survived for thirteen years from the time of diagnosis. It was plain that a better appreciation of the management of Addisonian crisis was also yielding good results for in the last five years out of 12 incidents of crisis there had only been 1 death. It had recently proved possible to rescue a patient suffering simultaneously from miliary tuberculosis and Addisonian crisis. 2 patients in the series had had successful pregnancies. Lastly, with the help of cortisone as well as DCA for maintenance treatment most of the surviving 16 patients were fit for some sort of employment and in 1 case for hard manual work.

Dr. S. Leonard Simpson (Consultant Endocrinologist, St. Mary's Hospital; Endocrinologist, Pædiatric Unit, St. Mary's Hospital): Before coming to my main theme of treatment, I wish to refer briefly to a few significant points not directly related to therapy.

(1) The clinical picture of more chronic Addison's tends to simulate Simmonds' disease, including very scanty pubic hair, apathy, inertia, negativeness, sensitivity to cold, slow pulse and tendency to hypoglycæmic coma. The clinical differential diagnosis at this phase may be difficult and the ACTH and epinephrine diagnostic tests equivocal. The sensitivity to cold in one fatal case was not associated with an atrophic thyroid. Although most features respond to cortisone, including even regrowth of pubic hair and improvement in scalp hair, the thyroid in Addison's disease may be atrophic or infiltrated with lymphocytes.

(2) Before the clinical picture of Addison's disease presents as a diagnostic entity, patients may have acute adrenal insufficiency in association with intercurrent infection or trauma. Some of these patients may never develop the conventional picture of Addison's disease. These considerations call for a therapeutic awareness, particularly in the presence of a tuberculous background. We know from partial bilateral adrenalectomy for hypertension and for Cushing's syndrome that a patient may appear normal with only a fraction of one adrenal gland remaining. The potential therapeutic role of physiological doses of cortisone in severe infections has been overshadowed by the harmful effects of continued large doses in disseminating localized lesions.

(3) A degree of spontaneous recovery has appeared to occur in 3 of my patients, in 1 with the climacteric. Hypertrophy of residual islets of adrenal cortex seems probable. Such patients need supplementary therapy in the presence of infection or during operative interference.

(4) I have recently (1953) recorded raised sedimentation rates in a proportion of Addison patients in the absence of obvious infection and their apparent reduction with cortisone. I indicated the need for further study and would like to indicate two qualifying factors: (*a*) minor or even occult infection which would not raise the sedimentation rate in normal people but does in patients with Addison's disease; (*b*) the hæmopoietic factor producing an increase in hæmoglobin, red cells, and hæmatocrit percentage. The question of a more direct hormonal influence remains for elucidation. Leslie Wilson (1953) has since recorded a raised sedimentation rate in Simmonds' disease and, in correspondence, indicated that in some of these patients there was no obvious infection. Further investigations are proceeding.

Therapy

My observations are based on more than 100 cases seen in the past twenty years, a third of which have come under personal observation for long periods.

I should like to treat therapy in historical sequence because I personally, and this Society, have played an intimate part in the various stages of development of our knowledge. Before coming to specific therapy, it would be prudent to emphasize the factor of anticipation and prevention, as estimates of a tuberculous basis for Addison's disease, that is, tuberculous destruction of the adrenals, vary from 60 to 80%. The prevention of tuberculosis generally will eliminate more than 50% of the incidence of Addison's disease.

Treatment with aqueous cortical extracts.—I was at the Mayo Clinic in 1930, as Research Fellow in Medicine, when the Swingle and Pfiffner extract became available to Dr. Leonard Rowntree. After seeing the first 3 cases treated and being convinced that a dramatic forward step had occurred, I returned to London that year with a limited supply of the extract given to me by Swingle and Pfiffner; and was fortunate enough to treat a patient in crisis—the first treated outside the Mayo Clinic—and to show the case to this Society (Simpson, 1930). I also reported briefly in the *Journal of Physiology* (1931). Rowntree and colleagues reported their results in 1931 and I recorded mine fully in the *Quarterly Journal of Medicine* in 1932, when I described 6 cases comprehensively investigated and treated, including treatment in crisis.

The chief difficulty with aqueous cortical extracts is the need for large volumes in severe cases, e.g. 30 ml. a day, and even 10 ml. a day is a cumbersome therapy over a long period. The extract, however, does contain many, if not all, of the cortical hormones.

Salt therapy.—The next important phase was the recognition in 1932 by Robert Loeb of the Presbyterian Hospital, New York, that Addison patients were benefited by salt by mouth and went into crisis if deprived of salt. His work was substantiated by experiments on adrenalectomized dogs with Atchley and Stahl (1935), and Loeb suggested that "the most attractive hypothesis which may be advanced at this time is that the adrenal cortex serves as a regulator of sodium metabolism." Loeb made an invaluable contribution by drawing attention to this aspect of adrenal function, but for the time being it tended to obscure other important functions which were uninfluenced by salt. Thus, in my 1932 paper, I emphasized the frequency of low blood sugars in chronic severe insufficiency as well as in crisis, and in subsequent papers indicated the

danger and frequency of hypoglycæmic episodes, not infrequently fatal. Nevertheless salt remains a valuable therapeutic weapon, especially when used supplementary to hormone therapy. In one of my cases, a naval officer in Hong Kong was brought out of crisis by cabled advice to give 20 grammes of salt a day by mouth and was successfully brought back to this country to survive many years on more modern therapy. Another case, a male of 46, an undoubted case with typical blood chemistry and pigmentation of mucous membranes, has remained well for sixteen years on salt therapy only, except for Eucortone during infection; and I have seen a similar case in South Africa. Salt is an emetic and few normal people could take 12 grammes a day. The ability to do so is almost confirmatory of the diagnosis, but some Addison's patients cannot take salt without nausea even though they need it, biochemically speaking.

Desoxycorticosterone acetate.—The next step was the synthesis of desoxycorticosterone by Reichstein in Zurich, and I happened to be the first clinician to record its clinical use by injection and by implantation. This was reported in the *Lancet* in September 1938. On December 13, 1938, I read a paper to the Section of Therapeutics of this Society, which was published in April 1939, dealing with 4 cases and the implantation method. Valuable papers were published by Thorn, Howard, Emerson and Firor in May, and by Thorn, Howard and Emerson in July 1939. I drew attention to the fact that in some patients the deoxycortone itself, or the oily solution in which it was contained (arachis or sesame), produced painful local lumps when it was injected subcutaneously or intramuscularly. Although it was effective in some patients in doses of 5 mg. daily, and salt enhanced its effect or permitted a reduction of its dosage, clinical and experimental observations indicated that it was not the only essential factor in adrenal function, the adrenalectomized marmot, for example, dying with a normal serum sodium and chloride and a very low blood sugar (Britton and Silvette, 1934). The effect of the implantation of 200 mg. of desoxycorticosterone acetate in the subcutaneous fat of the abdomen lasted some three months or more and maintained the patient in moderate health, supplementary salt or even injected desoxycorticosterone being necessary in some cases. It was noted that "the rate of absorption is probably constant and extra effort or exertion calls for supplementary therapy". By removing tablets and weighing them it was found (Simpson, 1939*b*) that 0·3 mg. was absorbed daily from a 50 mg. tablet. In numerous publications subsequently, the implantation dose recommended was 100 mg. for each 1·0 mg. of desoxycorticosterone injected and for prudence 100 mg. less than the total calculated. Thus for a patient needing 5 mg. of DOCA daily, the quantity implanted would be 400 mg. and this was found to last from six to eight months, and occasionally longer, being supplemented by salt after the first three months. It would appear that 1·0 mg. injected once daily was equivalent to 0·6 mg. gradually absorbed throughout the twenty-four hours.

I also drew attention in several publications to the danger of overdosage with deoxycortone, particularly with the method of implantation, and the prudence of maintaining the patients for several weeks on injections before calculating the dose for implantation and of making an initial implantation of not more than 300 mg. I would like to quote my summary on overdosage (1950) as follows:

"The effects of overdosage are seen both with the injection method and with the implantation method, but the former is much easier to correct than the latter, which necessitates removal of tablets. Overdosage leads to excessive retention of fluid and sodium, with increased excretion of potassium and low potassium serum concentration, resulting in weakness and paralysis of muscles, including the cardiac muscle. Other characteristic manifestations are superficial œdema of face and limbs, crepitations in the lungs, and enlargement of the heart, with or without pericardial effusion. The œdema, however, may not be conspicuous, and the excessive weakness or paralysis may be wrongly regarded as due to inadequate treatment. The blood chemistry may be deceptive in that the sodium and the chloride may be normal, but the serum potassium is usually low. Hypertension may be present initially with excessive fluid retention, but with cardiac failure this gives place to hypotension. Apart from the œdema of the cardiac muscle, multiple foci of necrosis in the heart have been found at necropsy. Electrocardiographic changes, with low serum potassium, are low-voltage Q.R.S. complexes, lowering, or inversion of the T waves, depression of the S–T segment, and prolongation of the Q.R.S. interval. Occasionally some patients show a more insidious chronic dry hypertension with this treatment, but, in the absence of the other features, this is not usually important and may tend to correct itself.

"The best treatment of overdosage in Addison's disease is removal of the implanted tablets, but as a preliminary emergency measure 100 ml. of 2% potassium chloride may be injected intravenously. If the dosage is properly calculated, however, implantation therapy is excellent, and since the effects last some eight months many patients prefer it to all other methods of treatment. As the effect of therapy wears off, the administration of salt by mouth may permit the postponement of further implantations from the sixth to the tenth month."

In relation to the prevention of overdosage with DOCA, I feel it necessary to express the view that George Thorn and his colleagues, who are continually contributing so much valuable and fundamental knowledge to the subject of adrenal function, have apparently erred in their

published calculation of equivalents for implantation. Thus, in the first paper published in America on this subject, they stated that for each 0·5 mg. of deoxycortone injected, one tablet of 125 mg. should be inserted under the skin. This formula has been followed very widely in America and in other parts of the world, and in my experience such heavy dosage is bound to lead to the complications of overdosage. This view is modified but not obviated by the prudent practice advocated by Thorn of waiting several weeks before arriving at the maintenance dose. I expressed this opinion several years ago at the Atlantic City Endocrine Conference and in "Major Endocrine Disorders". Thorn has told me that in actual practice we do not differ and that he usually employs implants of 300 to 400 mg. In his original 1939 publication, in 3 cases the implanted dose was 300 mg., in one case 420 mg., in one case 470 mg. and in one case 800 mg., the last 5 patients, however, having 12 grammes of salt daily as well. In a second 1939 paper, however, he speaks of daily requirements of deoxycortone by injection as 2 to 10 mg. with salt, or 10 mg. more without salt, and in his 1942 paper he states that the majority of patients require 5 mg. of DOCA, or less, with 4 grammes of salt daily; he also states that a supplementary therapy of 3 grammes of salt daily was always used when patients were prepared for pellet implantation but adheres to the formula of one pellet of 125 mg. being implanted for each 0·5 mg. of hormone so required by daily injection together with 3 grammes of salt daily. He also stated that these pellets "provided effective therapy in most patients for at least twelve months", a period which in my opinion is usually too long if you are to avoid overdosage initially. Thorn himself records that of 64 patients, 22 showed hypertension, 17 œdema including 3 with anasarca and 5 cardiac decompensation. He therefore appears to have met overdosage. In New York, Soffer *et al.* (1940) certainly recorded dangerous overdosage with Thorn's formula, even after stopping salt, and in 2 cases it was necessary for them to remove pellets. They conclude that "it is wiser to implant less than the required number of pellets".

In my 1939 paper to this Society (Simpson, 1939*a*) I also drew attention to an alternative and effective method of desoxycorticosterone acetate therapy, namely by inunction, using 20 mg. in 1 ml. of solution containing 100 mg. of benzyl alcohol. Rubbed in daily, preferably by the patient, this is as effective as 5 mg. injected, and some of my patients have used it for months successfully. The disadvantage is its high cost. Another possible alternative is the use of deoxycortone sublingually either in oily solution or as "linguets", a form of therapy which cannot be considered as constantly effective in severe cases but may prove useful as an adjunct to other methods.

More recently deoxycortone has been prepared in the form of trimethyl acetate of desoxycorticosterone "crystules" in buffered isotonic aqueous suspension prepared by Ciba. 50 mg. to 100 mg. can be injected in 2 ml. or in 5 ml. intramuscularly, preferably with some novocain. The "crystules" form a depot from which there is gradual absorption and in 2 of my patients the effect of 75 mg. to 100 mg. lasted some three to five weeks and was as effective as 5 mg. DOCA injected daily. The injections are sometimes painful and must be given slowly.

Although some patients appear to do quite well on deoxycortone, with or without salt, and are certainly very much better than without it, we should be ignoring our physiological knowledge if we were surprised at its inadequacy, at least in the more severe cases. The patients are very susceptible to infection and to hypoglycæmia; they lack energy and well-being; some tend to maintain, or initially gain, weight but others in the course of time lose weight progressively. They may become depressed, apathetic and negativistic. Part of the behaviour pattern may be associated with a chronic and intermittent hypoglycæmic state. More severe hypoglycæmia is manifested by coma, sometimes preceded by convulsions. Such severe hypoglycæmia may be precipitated by infection or undue stress and may be associated with disturbed mineral metabolism, but most of us with experience have been disquieted by the sudden onset—sometimes fatal—in patients who appear well and have had normal blood electrolytes the previous day. One patient was admitted to hospital from a hotel with an erroneous diagnosis of strychnine poisoning. Addison patients, like diabetics, should carry a card with them stating their condition and the possibility of their having hypoglycæmia as this is the most frequent cause of death under deoxycortone therapy. An idea of the inadequacy of DOCA is summed up by my review of 20 patients so treated whom I was able to follow up for a number of years. Of these 9 are alive and reasonably well, with an average survival of seven years and the longest ten years; 9 are dead with an average survival of three years, the longest being eight years; and 2 cannot be traced.

Lipoid adrenal extract.—This was first made by Upjohns some years ago from hog's adrenals. It was relatively rich in the carbohydrate regulation factor and 1 ml. of the oily solution was equivalent to 5–10 ml. of aqueous cortical extract. It was very expensive and not available in this country but in the absence of cortisone would have become of considerable use.

Liquorice.—Revers (1951) using liquorice for gastric ulcer noted the development of œdema and hypertension. Borst (1950) showed a DOCA-like action with retention of sodium and loss of potassium. Borst tried it on one case of Addison's disease without benefit but Groen *et al.* (1951) found a DOCA-like response in one case of Addison's disease. The formula of glycyrrhizonic acid, or rather its glucuronic acid component, is related to that of the deoxycortone group of steroids. Borst *et al.* (1953) now conclude that the DOCA-like action of liquorice

is only obtained when enough adrenal tissue is still operating or when the patient is also treated with cortisone.

Testosterone.—This in itself is of no use in Addison's disease, but, where the 17-ketosteroids are very low, testosterone or methyl testosterone is of value as supplementary therapy to deoxycortone. I have found them of greater value in females than in males and this is not unexpected as there is no appreciable gonad contribution to the total androgens in the female. If testosterone is implanted with DOCA it must be remembered that it has an additional fluid retention action.

Cortisone.—Cortisone first came into clinical prominence because of its effect on rheumatoid arthritis. However, the most rational application of cortisone therapy is in Addison's disease. Cortisone is known to cause, both in animal and in man, a systemic spread of local infection and particularly of tuberculosis. It was therefore natural that clinicians should have been wary of using cortisone in Addison's disease where there was a probable, or certain, tuberculous background. Nor can it yet be said with confidence that this danger of cortisone can be ignored. At the same time we must remember that patients with adrenal insufficiency, as well as adrenalectomized animals, are more susceptible to infection than normal people or animals; and that pulmonary tuberculosis may develop in a patient with Addison's disease in the absence of cortisone therapy. I am therefore inclined to the view that providing cortisone dosage is less than the normal daily physiological requirements of an individual there is little, or no, danger of tuberculous spread and, judging from completely adrenalectomized patients, physiological dosage would appear to be in the neighbourhood of 50 mg. Thorn writes me that he has had no example of tuberculous spread from the use of cortisone in Addison's disease in a large series of cases.

My own experience is only of 4 cases treated with doses of 12–25 mg. cortisone daily. The results are remarkably good. The patients gain in strength and well-being; their capacity for effort is amazingly increased; their weight is restored to normal or above normal; hypoglycæmic phases are abolished; their negative, apathetic and depressed Addisonian personality is changed back into their normal positive, active, interested and alert personality, perhaps with some euphoria; their appetite returns; they lose the tendency to develop minor infections easily; sub-normal values for hæmoglobin and erythrocytes are restored to normal, the percentage of neutrophils increases and the percentage of lymphocytes decreases so as to approach nomality; the blood pressure becomes normal, or above normal, the blood electrolytes may be maintained at normal or near normal levels and there may be a rise in the low alkali reserve. For electrolyte normality one patient required added salt and another desoxycorticosterone. A remarkable effect of cortisone in one of my patients was a reversal of the abnormal electrocardiogram, which latter may be found in some 40% of patients with Addison's disease in some phase. Thorn *et al.* (1951) reported this effect and that the abnormal slowed electroencephalogram of Addison's disease was restored to normality by cortisone.

In a paper last year (Simpson, 1952) I suggested on physiological grounds that cortisone was suitable for those cases of Addison's disease that failed to gain weight and strength and tended to have hypoglycæmic attacks. I would now take the view that when cortisone becomes available at economic prices and in quantity it will be the treatment of choice for Addison's disease. Cortisone may prove effective by itself but added salt or even deoxycortone may be necessary. Thorn *et al.* (1951) used 1 to 2 mg. DOCA daily in all cases as basic treatment, supplemented by cortisone. The convenience and comfort of the patient might be better suited, apart from costs and supplies, by the basic use of cortisone, with or without salt, supplemented where necessary by "crystules" injected monthly, or implantations at intervals of eight months, or perhaps by "linguets". Cortisone is easily given as tablets of 25 mg. each, half a tablet by mouth twice daily, and contrary to theoretical considerations some patients find one tablet daily more effective than a half twice daily. Cortisone may also be prepared as a medicine in suspension, or injected intramuscularly once daily, the latter effect being a steady one of slow absorption over the twenty-four hours, with a latent period of some hours. Criteria for judgment in combining and varying therapy emerge with the careful study of individual patients.

I have much pleasure in thanking Sir Harold Himsworth and the Medical Research Council for supplies of cortisone.

Treatment of crisis in Addison's disease.—The availability of cortisone is now recognized as the most important factor in crisis. Cortisone should be given by mouth when the patient can swallow as it acts very rapidly, and I have seen dramatic results within four hours. If not, it can be given by intramuscular injection in dosage of 100 mg. or more for some days. Since intramuscular cortisone is absorbed slowly, taking some hours to achieve its maximum effect, other measures such as intravenous saline and glucose are appropriate in the first case if the patient is *in extremis*. Cortisone may be given intravenously for more rapid action and no harm resulted on the few occasions I have so used it, although it is prepared as a suspension of minute particles. Cortisone has minimized the dangers and terrors of Addisonian crisis, and should be available for all medical centres for this purpose. The best treatment of Addisonian

crisis, however, is prevention and the best prevention is the use of cortisone—even small doses of cortisone—when the basic treatment is deoxycortone. Even so, a dose of 25 mg. daily may need to be doubled or quadrupled in the incipient phase of crisis to prevent the latter developing in the presence of infection or trauma.

Addison's Disease and Diabetes Treated by Cortisone Illustrating its Diabetogenic and Ketogenic Action (Case History)

K. W., male, aged 26. This is 1 of 3 cases of co-existing Addison's disease and diabetes that I described in 1949. Such cases tend to have very unstable blood sugars, varying sometimes between 1,540 mg. to 40 mg. and hypoglycæmic coma within twenty-four hours. However, the onset of Addison's disease in a patient with pre-existing diabetes mellitus reduces greatly the insulin requirements.

Briefly the patient at the age of 18 (1945) began to lose weight and at the age of 20 (February 1947) Addison's disease was diagnosed; Na 302, K 31, NaCl 440 mg. per 100 ml.; 17-ketosteroids 6 mg. per twenty-four hours. X-ray showed healed lesion in left subapical region. His father died of pulmonary tuberculosis, aged 37, and his father's sister died of abdominal tuberculosis at the age of 3. Sedimentation rate normal at this time, 3 mm. in one hour. Given 5 mg. DOCA daily; much better; Na 339, K 15, NaCl 577. 400 mg. DOCA implanted six months later following mumps; diabetes developed. Periodic implantations of DOCA followed in next five years. He had intermittent attacks of hypoglycæmia, sometimes with coma, responding to intravenous glucose. Insulin progressively reduced from 40 units to 12 units a day over the next two years. April 1951, 400 mg. DOCA implanted. In February 1952 had 200 mg. DOCA inserted (no implant subsequent to this).

Seen April 1952: B.P. 150/85; taking 8 units globin and 10 units soluble insulin; weight has remained at 9 st. 4 lb. but feels weak. Cannot cycle around a block of houses because of fatigue. Very exhausted walking 100 yards. Very poor and capricious appetite; lethargic, apathetic; typical pigment; very rarely shaves; pubic hair horizontal; having frequent attacks of hypoglycæmia.

August 7, 1952, admitted to St. Mary's Hospital for cortisone therapy, which commenced on August 29. Before cortisone: X-ray chest, no abnormality; E.C.G. normal; B.P. 125/90; glucose tolerance 108, 220, 246, 276 (two hours); 17-ketosteroids 8·3 mg. per twenty-four hours; Hb 80%; leucocytes 3,500, neutrophils 30%, lymphocytes 65%; electrolytes: sodium 143 m.equiv., potassium 4·3 m.equiv., chlorides 94 m.equiv., alkali reserve 55·1 vol. CO_2/100 ml., urea 36 mg.; sedimentation rate 25 mm. per hour (Westergren) in the absence of any obvious infection. Insulin requirements 4 to 12 units a day. Cortisone was given by mouth on August 29, August 30 and August 31, 12½ mg. twice daily in tablet form. The immediate effect of the cortisone was to cause a severe diuresis and ketosis and a need for much larger doses of insulin. The patient became dehydrated and drowsy and was on the verge of diabetic coma. The cortisone was reduced from 25 mg. to 12 mg. daily but much larger quantities of insulin were still necessary. The aggravating effect of cortisone on diabetes and ketosis was very dramatically illustrated.

September 1 to 11, 12½ mg. cortisone as tablet once a day. September 12 to October 30, 3 mg. six-hourly in solution by mouth, 12 mg. daily. October 31 to November 22, 3 mg. t.d.s. November 23, 4 mg. t.d.s.

Insulin.—Soluble insulin 6 units daily given on admission. August 27, globin insulin 6 units daily; August 30, globin insulin 10 units daily; August 31, globin insulin 14 units daily; September 3, soluble insulin 10 units b.d.

The dose of insulin was progressively increased daily to control the hyperglycæmia and ketosis caused by the cortisone. September 24, 40 units mane and 26 units nocte, both soluble insulin. November 16, one mixed injection: SI 28 units, ZPI 12 units; November 17, SI 24 units, ZPI 10 units; November 23, soluble insulin 24 units mane and 12 units nocte; increased to 40 units mane and 20 units nocte. December 15, discharged, simple insulin 46 units mane and 24 units nocte.

Chemical data.—The blood sodium and potassium were normal before cortisone and remained normal. The chloride, which was slightly subnormal, became normal. No extra salt was given during cortisone therapy. The alkali reserve rose slightly from 55 to 65 volumes per 100 c.c. The blood urea was little changed.

Blood changes.—Hb rose from 80 to 90% within three weeks; total leucocytes from 3,500 to 8,000; percentage neutrophils from 30 to 41 and after three months to 54, and percentage lymphocytes fell from 65 to 56 and later to 40%.

Sedimentation rate (Westergren).—The initial value on August 28, i.e. before cortisone, was 25 mm. per hour without any obvious infection; on September 2 it was 14 mm., on September 11, 3 mm., on September 15, 4 mm., on October 7, 5 mm., on October 17, 8 mm. and on November 10, 10 mm. There appears to have been a definite reduction and then some increase from the lowest values.

Complicating attack of pyrexia.—On October 22, he developed an acute febrile episode, 103° F., with anorexia, malaise and shivering. Blood culture sterile. No obvious cause. Treated by penicillin and streptomycin for five days. Complete recovery. On December 7 another similar episode, treated in same way for three days with similar effect. No such episodes since. Left hospital December 15, 1952.

Subsequent progress.—Seen by me on Feburary 20, 1953. Taking 12 mg. cortisone by mouth in divided doses 3 mg. t.d.s., 50 units soluble insulin and 24 units zinc protamine insulin in one injection each morning, a diet of 3,000 calories total and 300 grammes carbohydrate. The patient looked very well indeed and quite different from pre-cortisone days. His face was full and his eyes not sunken. The pigment had decreased including that of the lips. He had gained some weight, was feeling very much stronger, appeared cheerful, alert, and active and interested. He stated that his "general increase in energy was most remarkable". Whereas previously he was distressed by walking 100 yards, he could now walk 2 miles with ease and could travel freely anywhere. B.P. 122/80, P. 70. He had no hypoglycæmic attacks. His urine was blue or green except at midday when it was brown. No extra salt given during cortisone therapy. Dr. R. R. H. Lovell and Dr. E. S. Snell of the Medical Unit, St. Mary's Hospital, collaborated throughout in the care and investigations of this patient.

REFERENCES

BORST, J. J. G. (1950) *Ned. Tijdschr. Geneesk.*, **94**, 3608.
——, TEN HOLT, S. P., DE VRIES, L. A., and MOLHUYSEN, J. A. (1953) *Lancet*, i, 657.
BRITTON, S. W., and SILVETTE, H. (1934) *Amer. J. Physiol.*, **107**, 190.
GROEN, J., PELSER, H., WILLEBRANDS, A. F., and KAMMINGA, C. E. (1951) *New Engl. J. Med.*, **244**, 471.
LOEB, R. F. (1932) *Science*, **76**, 420.
——, ATCHLEY, D. W., and STAHL, J. (1935) *J. Amer. med. Ass.*, **104**, 2149.
REVERS, F. E. (1951) *Ned. Tijdschr. Geneesk.*, **95**, 120.
ROWNTREE, L. G. (1947) *Acta med. scand.* Suppl. 196, 92.
——, GREENE, C. H., BALL, R. G., SWINGLE, W. W., and PFIFFNER, J. J. (1931*a*) *J. Amer. med. Ass.*, **97**, 1446.
——, ——, ——, ——, —— (1931*b*) *Trans. Ass. Amer. Phycns.*, **46**, 123.
SIMPSON, S. L. (1930) *Proc. R. Soc. Med.*, **24**, 497.
—— (1931) *J. Physiol.*, **72**, 4.
—— (1932) *Quart. J. Med.*, N.S., **1**, 309.
—— (1938*a*) *Lancet*, ii, 557.
—— (1938*b*) Major Endocrine Disorders: London. (2nd ed., 1948.)
—— (1939*a*) *Proc. R. Soc. Med.*, **32**, 685.
—— (1939*b*) *Practitioner*, **143**, 502.
—— (1946) *Proc. R. Soc. Med.*, **39**, 511.
—— (1950) *Brit. med. J.*, ii, 1164.
—— (1952) *Brit. med. J.*, i, 725.
—— (1953) *Proc. R. Soc. Med.*, **46**, 39.
SOFFER, L. J., ENGEL, F. L., and OPPENHEIMER, B. S. (1940) *J. Amer. med. Ass.*, **115**, 1860.
THORN, G. W., DORRANCE, S. S., and DAY, E. (1942) *Ann. intern. Med.*, **16**, 1053.
——, FORSHAM, P. H., FRAWLEY, T. F., WILSON, D. L., RENOLD, A. E., FREDRICKSON, D. S., and JENKINS, D. (1951) *Amer. J. Med.*, **10**, 595.
——, HOWARD, R. P., and EMERSON, K. (1939) *J. clin. Invest.*, **18**, 449.
——, ——, ——, and FIROR, W. F. (1939) *Bull. Johns Hopk. Hosp.*, **54**, 339.
WILSON, L. A. (1953) *Lancet*, i, 203.

Dr. E. N. Allott (Pathologist, Lewisham Group Laboratory): The modern chemical outlook on Addison's disease dates back some twenty-five years, from the demonstration by Marine and Baumann in 1927 that the life of adrenalectomized animals could be prolonged by administration of sodium chloride, and the preparation in 1930 by Swingle and Pfiffner of an extract of suprarenal cortex capable of relieving symptoms of adrenal insufficiency. From these adrenal

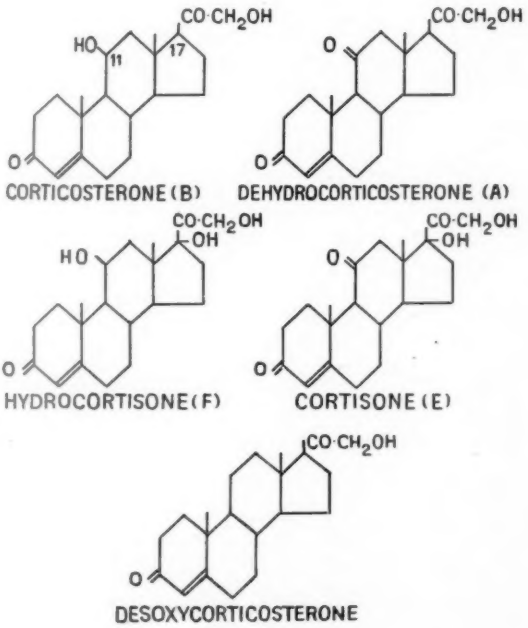


FIG. 1.

extracts, a very large number of steroids have been isolated and characterized, mainly through the work of Kendall and his colleagues at the Mayo Clinic and of Reichstein in Switzerland.

The function of the anterior pituitary in controlling the activity of the adrenal cortex, from the early work of Collip in 1933, could be studied much more easily as more potent adrenotrophic hormones were prepared by Li and by Sayers in 1943; this hormone has been prepared in peptide form by Li and by Morris since 1950.

Fig. 1 shows the constitution of some of the compounds which have been isolated from adrenal cortex, but until recently there was always doubt as to which of these (and other) compounds were actually formed by the suprarenal, and which were artefacts, produced in the chemical manipulations necessary for isolation.

Recent work by Pincus and his colleagues has clarified this position: by perfusing freshly excised adrenals with blood to which corticotrophin (ACTH) had been added, isolating the steroids and submitting them to paper chromatography, all the steroids shown in Fig. 1 were identified, as well as some ten other steroids in various amounts, presumably corresponding to the physiologically active "amorphous fraction" of Kendall. Table I, modified from Pincus, Hechter and Zaffaroni (1951), shows the results obtained.

TABLE I.—STEROID FORMATION IN ACTH PERFUSED ADRENAL GLAND

	μg. per 2 litres
Corticosterone (B)	1,200
Hydrocortisone (F)	1,000
Dehydrocorticosterone (A)	250
Cortisone (E)	120
Desoxycorticosterone	120
About 10 unidentified steroids ..	*ca.* 1,000

(Pincus, Hechter and Zaffaroni, 1951)

From this work, it appears that cholesterol is the initial source of steroids and that of the 11-oxysteroids, 17-hydroxycorticosterone (hydrocortisone) and corticosterone, which are formed in largest amount, are the primary products rather than cortisone, for in other experiments, if the 11-desoxy derivatives of these were perfused, an OH group was inserted in position 11, and 11-hydroxy products were not further changed: further, compounds such as progesterone and prenenolone are converted by perfusion of adrenals into more highly oxygenated compounds, notably the two already referred to. In agreement with this, hydrocortisone (compound F) has been isolated from the urine of patients excreting large amounts of steroid under ACTH therapy (Sprague *et al.*, 1950).

In the urine are excreted large numbers of steroids, some belonging to the C_{21} group (with 21 carbon atoms) to which belong all those shown in Fig. 1, but many belonging to the C_{19} group, without the $CO\text{-}CH_2OH$ chain at C_{17}. Fig. 2 illustrates the difference: it is important

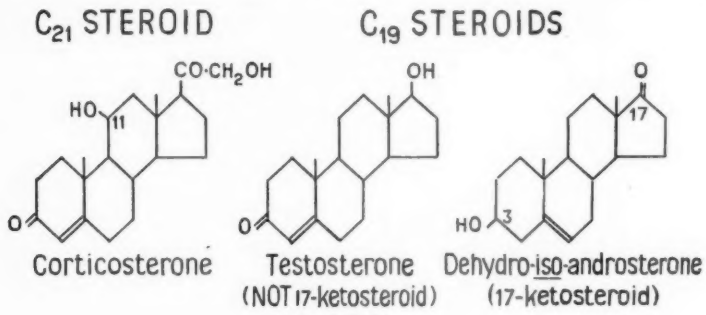


FIG. 2.

to recognize the C_{19} steroids, which include the 17-ketosteroids, are not adrenal hormones, but are formed by breakdown of these, possibly in the liver.

Unfortunately, technical estimation of the corticosteroids is much more difficult than that of the 17-ketosteroids: the former are largely excreted as conjugation products, and in the hydrolysis of these much steroid is destroyed and much more work has been published on the 17-ketosteroids. In Addison's disease the excretion of 17-ketosteroid falls to very low values (0·1–8·6 mg./day, average 3·0, in the female and 1·0–8·0 mg./day, average 4·0, in the male) (Thorn *et al.*, 1949). As a few mg. in the male are contributed by the testis, a value near zero might suggest a hypopituitary origin, rather than a primary adrenal disorder. The reported normal values

for corticosteroids vary according to the technique employed, but whatever method is used, very low values are found in Addison's disease.

The hormone secretion of the adrenal is under the control of the anterior pituitary, and when the normal gland is stimulated by ACTH there is considerable rise in excretion both of 11-oxysteroids and of 17-ketosteroids. Although, as shown by comparing the results in two different methods of assay, enlargement of adrenal in hypophysectomized animals, and depletion of ascorbic acid in adrenals, it would appear that there may be two different anterior pituitary hormones, there is little to support Selye's ideas of a multiplicity of hormones, and that the adrenal gland secretes not only varying amounts but a very varied proportion of different steroids according to demand.

The administration of ACTH to the Addisonian patient, of course, produces little or no rise in the excretion of corticoids or 17-ketosteroids.

When anterior pituitary stimulation is lacking, as in complete Simmonds' disease, the adrenals appear continuously to secrete small quantities of hormone, and the blood electrolyte composition remains reasonably normal, but they are incapable of responding to stress. When ACTH is given to a patient with Simmonds' disease, the results are variable: there may be eventually a marked rise in corticoid and 17-ketosteroid excretion, but it is much slower than normal.

The rate of ACTH secretion is partly controlled by the level of cortisone in the blood, and if cortisone is given to a normal individual, in reasonable doses, there is a fall in 17-ketosteroid excretion, through anterior pituitary inhibition and consequent lower endogenous formation of steroids: in the Addisonian patient, by contrast, where the endogenous steroid formation is negligible, cortisone leads to an appreciable rise both in 17-ketosteroid and corticoid excretion.

The physiological actions of the different adrenal steroids fall broadly into two classes: those containing $-OH$ or $=O$ on the 11 carbon atom have powerful effects on carbohydrate metabolism, but in small doses comparatively little on that of the electrolytes, whereas DOCA, without this 11-oxygen, has pronounced effects on mineral metabolism, but comparatively little on carbohydrate.

Insufficient clinical evidence is available at present to distinguish fully between the actions of the different 11-oxysteroids, but it is perhaps not surprising that the apparent primary product of the adrenal, compound F (hydrocortisone), appears to have greater activity in local application to joints and eye than cortisone (compound E), though in systemic administration they resemble each other closely: compounds A and B appear to have no anti-rheumatic effect, and very much less effect on carbohydrate metabolism than cortisone or hydrocortisone: but they have a more powerful salt-retaining action than cortisone, and seem to be efficient agents in Addison's disease.

As regards the metabolism of carbohydrate, the effect of lack of 11-oxysteroids is a low fasting blood sugar, hypersensitivity to insulin, and poor glycogen storage. These changes are reversed by administration of 11-oxysteroids, and the use of these in excess may exaggerate a pre-existing diabetes or even bring on a diabetic condition: these changes are usually reversible, and in therapeutic doses cortisone very rarely has significant effect on the carbohydrate metabolism of a normal individual.

Important as these effects are, they are of less significance than the effects on mineral metabolism of lack of the salt-retaining steroids: an adrenalectomized animal can have its life much prolonged by use of salt and water, but the use of glucose to remedy the hypoglycæmia has little effect in prolonging life. Nevertheless, cortisone alone in some cases of Addison's disease has enough salt-retaining action to be an efficient therapeutic agent.

The characteristic blood electrolyte changes in Addison's disease are, of course, a rise in the serum potassium and urea, and a fall in the sodium and chloride (and also in the bicarbonate): Thorn has suggested that a serum sodium below 136 m.Eq/lit. with a sodium/potassium ratio below 30, suggests adrenal cortical insufficiency; however, not all cases of Addison's disease in the chronic stage show these changes, and it is possible to have a patient showing symptoms of Addison's disease, with a perfectly normal blood chemical picture.

A low serum sodium and chloride level is not uncommon in many other diseases, such as nephritis and infections, but the characteristic change in Addison's disease is the maintenance of a high urinary sodium and chloride concentration while there are low levels in the serum: in most of these other conditions, the concentration in the urine is low, and this is, of course, made use of in the second part of the Kepler test for adrenal function. However, even this combination of changes is not confined to adrenal insufficiency: among others some cases of tuberculosis and rare cases of "salt-losing nephritis" show the same changes.

The chemical changes can be restored towards normal by treatment with DOCA, cortical extract, or in some cases by the use of salt alone. In my experience, the urea and potassium tend to rise and fall together, and rise in potassium and urea is a more sensitive indicator of approaching adrenal failure and occurs earlier than changes in the sodium and chloride levels.

Recently Frawley and Thorn (1951) have shown that the saliva, although a hypotonic fluid, of the Addisonian patient, like the urine, tends to have relatively high sodium concentration: the potassium content remains relatively constant, and the sodium/potassium ratio is consequently higher than normal. Table II shows the range found by Frawley and Thorn in different

TABLE II.—SALIVARY Na/K RATIO (IN M.EQ.)

Normals	0·3–2·1, mean	1·3
Untreated Addison's	2·2–8·1, „	5·0
Cushing's syndrome	0·2–1·2, „	0·5

(Frawley and Thorn, 1951)

conditions. The authors mention that if serum sodium is very low (say below 132 m.Eq.), the salivary sodium may not be high enough to give a raised ratio, but in these cases the blood findings will probably give the required information.

The characteristic of the kidney in the adrenal-deficient subject, as already mentioned, is to excrete a urine with a relatively constant composition and high sodium and chloride concentration. The kidney reacts only comparatively slowly to change in internal environment: this partly explains why it is possible to raise sodium and chloride levels towards normal by the addition of salt to the diet: added intake of salt by a normal individual has very little effect on his serum composition. Similarly, if a test dose of water is given to the Addisonian patient, the kidney responds only slowly, and an abnormally small proportion of a test dose of 20 ml. per kg. is excreted in four hours: this is, of course, the basis of Part I of the Kepler test.

If a patient is treated with deoxycortone, the power to conserve sodium and chloride and to excrete potassium and urea is rapidly restored, but water diuresis remains still imperfect, and indeed little changed by this hormone. On the other hand, comparatively small doses of cortisone, say 25 mg. given by mouth three to four hours before the water, promptly restore the diuresis to normal, both in Addisonians and patients with Simmonds' disease. Fig. 3 shows the restoration

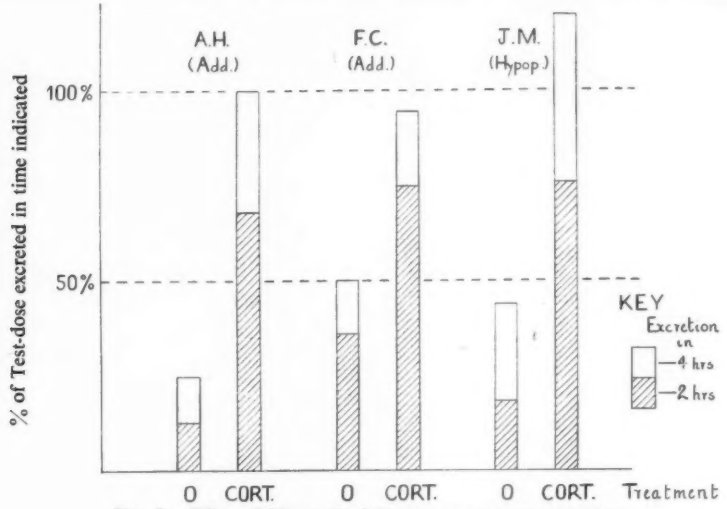


FIG. 3.—Effect of 25 mg. Oral Cortisone on Water Excretion.

to normal of water excretion in 2 cases of Addison's disease and 1 of hypopituitarism. Garrod and Burston (1952) have shown that part of this effect at any rate is due to raising the low renal blood flow and glomerular filtration rate. Whether the neutralization of an antidiuretic hormone is also involved is not definite.

It might be thought that the effect of ACTH might differentiate between a primary adrenal failure (Addison's disease) and a primary pituitary one (Simmonds' disease): up to the present, my experience with ACTH in water diuresis has been so variable that I would not like to make any generalization, and other recorded experiences are equally variable.

REFERENCES

FRAWLEY, T. F., and THORN, G. W. (1951) *Proceedings of the Second Clinical ACTH Conference* (ed. J. R. Mote). London; **1**, 115.

GARROD, O., and BURSTON, R. A. (1952) *Clin. Sci.*, **11**, 113.

PINCUS, G., HECHTER, O., and ZAFFARONI, A. (1951) *Proceedings of the Second Clinical ACTH Conference* (ed. J. R. Mote). London; **1**, 40.

SPRAGUE, R. G., POWER, M. H., MASON, H. L., ALBERT, A., MATHIESON, D. R., HENCH, P. S., KENDALL, E. C., SLOCUMB, C. H., and POLLEY, H. F. (1950) *Arch. intern. Med.*, **85**, 199.

THORN, G. W., FORSHAM, D. H., PRUNTY, F. T. G., BERGNER, G. E., and HILLS, A. G. (1949) *Ann. N.Y. Acad. Sci.*, **50**, 646.

Dr. A. W. Spence: *Deoxycortone trimethyl acetate in Addison's disease.*

Before describing our results with a long-acting preparation of deoxycortone in the treatment of Addison's disease, I should like to state that I entirely agree with Dr. Leonard Simpson's opinion that the implantation of 125 mg. of deoxycortone acetate for each 0·5 mg. injected daily, as advocated by American investigators, is far too high and liable to result in heart failure and death. I agree that not more than 100 mg. should be implanted for each 1·0 mg. of deoxycortone acetate in oil injected daily—in fact, I would go further and say 80 mg. for 1·0 mg. injected.

Sublingual therapy, in my experience, is useful in the treatment of mild cases, for injections and implantations are thus avoided. It is not a very practicable method of treatment, however, in the severer cases because about three times the intramuscular dose is necessary.

In collaboration with Dr. H. J. B. Galbraith and Dr. J. S. Jenkins I have recently been carrying out a therapeutic trial with a microcrystalline suspension of deoxycortone trimethyl acetate in isotonic buffered aqueous solution, generously supplied by the Ciba Laboratories, Ltd. We have, so far, used the preparation in 2 patients with Addison's disease:

Case 1.—A man, aged 35, maintained on deoxycortone acetate in oil in doses of 5 mg. intramuscularly on alternate days, his B.P. on this dose being 114/78. In November 1951, to determine the efficacy of deoxycortone trimethyl acetate, treatment was stopped until evidence of adrenal insufficiency appeared, namely, nausea, weakness, and a fall of B.P. to 100/50. 5 mg. of deoxycortone trimethyl acetate, injected intramuscularly, had little effect on his condition. Four days later the injection of 20 mg. caused rapid improvement, which was maintained until the eleventh day after the injection, when nausea returned and the B.P. fell to 95/64. This was taken as the end-point of the action of the preparation.

We now realized that higher doses of the preparation were necessary, but further treatment on these lines had to be postponed. 200 mg. of deoxycortone acetate were therefore implanted subcutaneously and the patient was discharged from hospital.

On Jan. 1, 1953, the patient was readmitted. During the previous year the action of the implants had, of course, ceased and his private doctor had treated him with daily injections of 4·0 mg. deoxycortone acetate. On Jan. 31, 100 mg. deoxycortone trimethyl acetate were injected intramuscularly and the daily injections of deoxycortone acetate were continued for four days (two days would have been sufficient) as the absorption of the trimethyl preparation may be somewhat delayed. His condition remained satisfactory (B.P. 120/80) thirty-five days after the injection of deoxycortone trimethyl acetate. No added salt was ever given (Fig. 1).

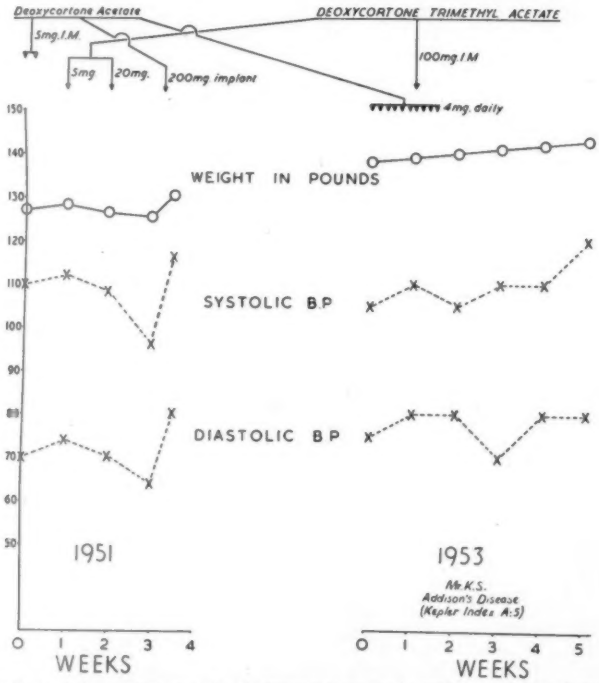


FIG. 1. (*Case* 1).—Effect of deoxycortone trimethyl acetate on body weight and blood pressure in Addison's disease.

Case 2.—A woman, aged 40. Admitted Sept. 3, 1952, receiving a daily dose of 5 mg. deoxycortone acetate intramuscularly. On this she had been feeling weak, wt. 8 st. 5 lb. and her B.P. varied from 90/50 to 105/80. Treatment was withheld for a few days; her wt. was 8 st. 1 lb., B.P. 96/78, serum sodium 310 mg. per 100 c.c. An intramuscular injection of 50 mg. deoxycortone trimethyl acetate did not improve her condition and during the next eight days she became lethargic and cold, lost 2 lb. in wt. (7 st. 13 lb.) and the B.P. fell to 80/50. Daily injections of deoxycortone acetate were re-started and she was stabilized on 7·0 mg. daily. She gained 8 lb. in two weeks (weight 8 st. 7 lb.), B.P. 108/70, and there was marked subjective improvement.

On Oct. 20, she was given an intramuscular injection of 150 mg. deoxycortone trimethyl acetate and the injections of deoxycortone acetate were stopped. After an initial fall the wt. was maintained at 8 st. 5 lb. and B.P. at 105/65 for the next twenty-eight days, but there was incomplete relief of symptoms during this period.

On Nov. 18, 200 mg. deoxycortone trimethyl acetate were injected with marked subjective improvement and she was sent home.

Dec. 18, although feeling very well, B.P. 106/68 and wt. 9 st. 1 lb., she was given another 200 mg. deoxycortone trimethyl acetate. Jan. 8 the serum sodium had risen to 345 mg. per 100 c.c., B.P. 120/66; Jan. 15, face a little puffy, slight œdema of ankles and blood pressure 140/80; Jan. 22 (thirty-five days after the last injection), feeling very well, wt. 9 st., B.P. 140/80, no œdema of ankles; 150 mg. deoxycortone trimethyl acetate injected. Thirty-one days later her condition, wt. and B.P. were satisfactory and she was given another 150 mg. No added salt was ever given (Fig. 2).

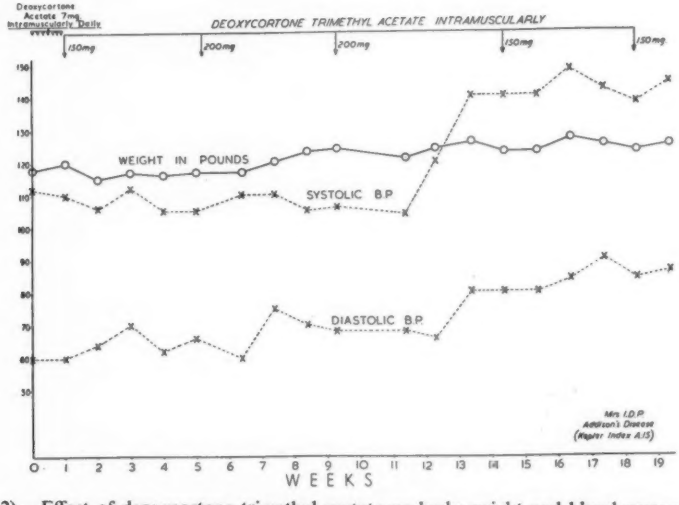


FIG. 2 (*Case* 2).—Effect of deoxycortone trimethyl acetate on body weight and blood pressure in Addison's disease.

Conclusions.—(1) Deoxycortone trimethyl acetate, when given in the correct dosage, exerts its action for at least five weeks. As the second patient was a fairly severe case and had had rather a bad time, we refrained from waiting until the action of the preparation had subsided in order to determine its exact duration, but contented ourselves with giving her monthly injections before symptoms of deficiency appeared.

(2) Our original doses were obviously too low and even a dose of 50 mg. in Case 2 had little effect. As absorption is slow, with too small a dose, an adequate blood level may not be obtained, or may be short-lived; thus, 20 mg. produced improvement for only ten days in Case 1.

(3) Patient should first be stabilized with daily injections of deoxycortone acetate. The initial dose of deoxycortone trimethyl acetate necessary appears to be about 30 times the daily dose of deoxycortone acetate injected intramuscularly. This assessment agrees with that of Thorn and Jenkins (1952). Subsequent doses, if given at monthly intervals, should be reduced, because all of the previous dose has not been absorbed. Thorn and Jenkins (1952) found that the average dose was 60 to 90 mg.; our higher doses in Case 2 were because the degree of adrenal insufficiency was fairly severe.

(4) The advantages of treatment with long-lasting preparations of this type over the implantation method are that surgical procedures are avoided, patients do not have to be readmitted to hospital for re-stabilization as they do before each implantation, and greater control can be attained by adjusting the monthly dose.

REFERENCE: THORN, G. W., and JENKINS, D. (1952) *Schweiz. med. Wschr.*, **82**, 697.

Dr. R. I. S. Bayliss agreed that in many instances the diagnosis of Addison's disease could be made on clinical grounds alone. In some cases additional diagnostic aid was necessary and because most of the proposed tests were indirect indices of adrenocortical function, he had estimated, in conjunction with Drs. Steinbeck and Hunter, the level of 17-hydroxycortico-

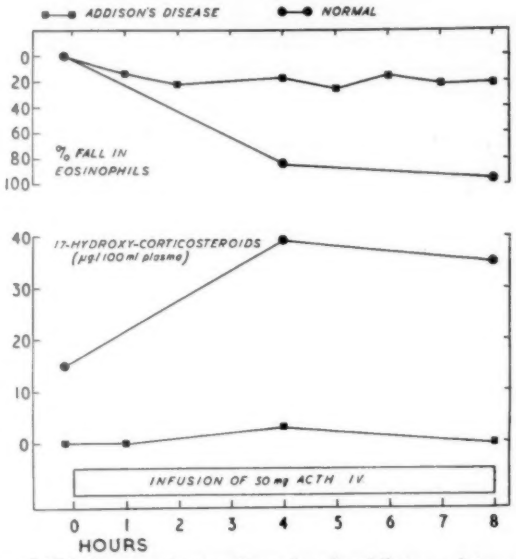


FIG. 1.—The response of 17-hydroxycorticosteroids and eosinophils to an intravenous infusion of 50 mg. ACTH over an eight-hour period in a normal subject and in a patient with Addison's disease.

steroids in the plasma of Addisonian patients. In normal subjects the range is 5–15 μg./100 ml. by their method and in Addisonian patients zero values were obtained. Furthermore, in contrast to normal subjects, there was no rise in the steroid level when 50 units ACTH were infused over an eight-hour period (Fig. 1).

REFERENCE: BAYLISS, R. I. S., and STEINBECK, A. W. (1953) *Biochem. J.*, **54**, 523.

Dr. R. R. de Mowbray (Guy's Hospital, London): In the diagnosis of Addison's disease the Thorn test is not reliable, in our experience at Guy's Hospital. 2 severe cases have shown an eosinophil response of more than 50% to a single injection of 25 mg. ACTH. In some cases the initial eosinophil count is so low that the significance of a fall in the number of cells is difficult to assess. We find that the eosinophil counts fluctuate considerably without the administration of ACTH, and we now consider it necessary to perform daily counts at the same time of day (e.g. about midday) for a whole week, giving 25 mg. ACTH, preferably by intravenous infusion over a period of twelve hours, between the third and fourth eosinophil counts. It is also desirable to estimate the 17-ketosteroid excretion during each twenty-four-hour period. Thereby the spontaneous fluctuations in adrenal cortical activity can be taken into account in assessing the response to ACTH.

In treatment we perform implantations of 200 to 300 mg. DOCA regularly every 6 months, without attempting to calculate the dose accurately. By this means we maintain our patients in good general health, without any need of extra salt intake, and the vast majority are able to continue their normal work. Since we instituted this treatment three years ago, crises have been almost completely eliminated. 7 patients have so far survived for periods of from eight months to seven years (average four years) from the onset of symptoms, compared with an average duration of eighteen months from onset of symptoms until death, before this treatment was instituted as a routine. 3 patients have, however, died three to four years after the onset of symptoms, as a result of tonsillitis leading to a virulent bronchopneumonia, with no response to antibiotics and intensive treatment with adrenal cortical extract. These patients showed evidence of adrenal crisis only terminally; the picture was one of lack of resistance to infection, suggesting some failure of antibody-formation.

During the past four months we have given, in addition, 12·5 mg. cortisone daily by mouth. Most of the patients have noted an increase in appetite and physical energy and in several cases

mouth-pigmentation has diminished or actually disappeared. The effect on ultimate prognosis and particularly upon the resistance to infection, is awaited with interest.

Dr. Arnold Woods (St. George's Hospital, London): Recently a man aged 29 was admitted to St. George's Hospital under Dr. C. B. Levick following a hæmatemesis and malæna. For one month previously he had complained of epigastric pain one hour after meals. He was extremely restless and unusually irritable and although there was marked hypotension (B.P. 70/25), there was evidence of only slight anæmia. The presence of a faint generalized brown pigmentation, with involvement of the gums and the buccal mucous membrane, suggested the diagnosis of Addison's disease, and a further history was elicited of weakness, lassitude, anorexia and loss of weight for eighteen months; blood electrolyte figures later supported the diagnosis. In spite of 80 c.c. Eucortone in an intravenous saline transfusion in four hours, the blood pressure became unrecordable and the patient lapsed into unconsciousness. Cortisone was then started, the response being dramatic, and 1·1 gramme was given in ten hours until the blood pressure had risen to 105/70. Subsequently Eucortone was given intravenously in amounts of 80–120 c.c. daily. The improvement was maintained until the occurrence of further hæmatemeses on the second and third days. The worsening of his clinical state was only temporarily controlled by blood transfusion, and there was later evidence of further intra-abdominal bleeding. Although the electrolyte balance had rapidly been restored and was maintained within normal limits, his condition deteriorated, he developed thrombophlebitis of his leg, and he died on the eighth day. The post-mortem examination showed almost complete atrophy of both adrenal glands and a large gastric ulcer.

It seems possible that the administration of cortisone contributed to the subsequent recurrence of bleeding from the gastric ulcer, but the desperate clinical condition in spite of the use of Eucortone appeared to demand that this risk should be taken.

Dr. G. A. Smart (Reader in Medicine, University of Durham): I should like to make just two points. The first is the use of ACTH in the diagnosis of Addison's disease. I have found that the four-hour test described by Thorn is not very reliable and, indeed, can be distinctly misleading. As an illustration I can quote two cases with obvious Addison's disease where an attempt was made to combine a modification of the four-hour test with a forty-eight-hour test. During two control days urine was collected for twenty-four-hour 17-ketosteroid estimation and eosinophils were counted at 10 a.m. and 4 p.m. on each day. ACTH was given at a dosage of 25 I.U. six-hourly, starting at 6 a.m. on the first test day. Eosinophils were counted at 10 a.m. and 4 p.m. on each of the days of ACTH administration and urine was collected for 17-ketosteroid assay on each of those days. For this purpose a "day" was considered to begin and end at 6 a.m. The table shows the results obtained in these 2 cases. It can be seen that the

			Case 1		Case 2	
			Eosinophils per mm.³	Urinary 17-ketosteroids mg./24 hrs.	Eosinophils per mm.³	Urinary 17-ketosteroids mg./24 hrs.
Control	1	10 a.m.	331	2·0		8·1
		4 p.m.	250			
	2	10 a.m.	380	1·5	150	4·6
		4 p.m.	381		147	
ACTH	3	10 a.m.	81	1·4	87·5	4·5
		4 p.m.	200		131	
	4	10 a.m.	644	0·9	200	3·7
		4 p.m.	578		250	

eosinophil estimation performed four hours after the first injection of ACTH is more than 50% lower than the corresponding estimation on the previous days and if this were the only index to be used, the diagnosis of Addison's disease would not be made.

The second point I wish to make is on the question of serum potassium levels in Addison's disease. The possibility of potassium intoxication as a factor which might, at times, be present in Addisonian crisis is not often mentioned.

I was recently privileged to see a case of Dr. G. O. Richardson's at Newcastle in which there was a voluntary muscle paralysis associated with a very high serum potassium level; details of this case are being published by Dr. Richardson. I mention this since the condition must have been overlooked in the past and since, if it is not dealt with promptly, it is liable to lead to death.

JOINT MEETING No. 1

Section of Pathology with Section of Medicine

Chairman—Professor G. PAYLING WRIGHT, D.M., F.R.C.P.
(President of the Section of Pathology)

[*December* 10, 1952]

DISCUSSION ON CHEMOTHERAPY OF TUBERCULOSIS [*Abstract*]

Professor R. Knox:

Isoniazid: In Vitro *Sensitivity and Resistance*

In the last few months we have been studying the sensitivity and resistance of *M. tuberculosis* and other mycobacteria to isoniazid. The work has been undertaken jointly with my colleagues Dr. Anderson, Dr. Collard, Dr. King and others, and I should like to mention a few of the salient points which we have established or which we are investigating.

(1) In Vitro *Tests of Sensitivity and Resistance*

We have previously shown (Knox, King and Woodroffe, 1952) that when a set of tubes of Dubos liquid medium containing falling dilutions of isoniazid is inoculated with *M. tuberculosis* the end-point shifts as incubation continues. We have shown that this shift in the end-point is the resultant of two factors—(i) inactivation of the drug which occurs even in uninoculated Dubos medium and (ii) the emergence of resistant organisms. The phenomenon of shift in the end-point could clearly be explained by either or both of these factors. If the drug were solely bacteriostatic then the growth which eventually occurred would be due to multiplication of the inoculated sensitive cells escaping from the influence of the drug as it became inactivated. If the drug were bactericidal to sensitive cells then the growth which eventually occurred would be due to multiplication of a few resistant cells which had survived in the inoculum. The truth probably is that both of these processes are important, and there is clearly a need for careful population studies on this problem. In the meantime it would seem that isoniazid in very high concentrations has a predominantly bactericidal action but is predominantly bacteriostatic in lower concentrations. The relative importance of the two effects will clearly depend on other factors besides drug concentration. We have evidence, for example, suggesting that sublethal concentrations of streptomycin increase the bactericidal effect; a similar increase in bactericidal efficiency is produced by increasing the temperature of growth (Knox *et al.*, 1952). That this effect of temperature is biologically important is suggested by the results obtained by Goulding and Robson in experimental tuberculosis (Goulding and Robson, 1952).

(2) *The Value of* In Vitro *Techniques*

We have developed a plate test using *M. smegmatis* as the test organism for investigations into the action of isoniazid and related drugs. A culture of *M. smegmatis* is heavily cultured on to the surface of an agar plate (using Dubos medium) and blotting-paper strips soaked in solutions of isoniazid or other substances under investigation are placed on the plate.

The smegma plate is useful for demonstrating:

(*a*) The relative efficiency of different drugs.
(*b*) The development of resistant strains.
(*c*) The suppression of resistance (e.g. by combination of isoniazid with streptomycin).
(*d*) Antagonism and synergism.
(*e*) Growth-stimulating substances.

We have recently described this technique (King, Knox and Woodroffe, 1953), which is essentially the auxanographic technique first used by Beyerinck (1889) and elaborated by Pontecorvo (1949).

(3) *The Significance of Resistance*

We have found that a strain of H37Rv which had developed resistance to about 10–20 μg./ml. of isoniazid produced typical corneal lesions in experimental animals (Goulding, King, Knox and Robson, 1952). These lesions did not respond to isoniazid. From patients with pulmonary tuberculosis whose clinical condition was deteriorating we have also isolated cultures of tubercle bacilli with similar *in vitro* resistance. On the other hand cultures from patients treated with isoniazid and streptomycin together have either proved negative or when positive have so far proved sensitive to both drugs after much longer periods of treatment. It looks therefore as though *in vitro* tests of resistance to isoniazid have some clinical significance, though the whole problem is complicated by various problems of bacterial nutrition.

(4) It is already established that isoniazid readily penetrates into tissues and cells. In this connexion it is well to remember that isoniazid has a smaller molecular weight than almost any other comparable drug. Its molecular weight of 137 compares, for example, with 172 for sulphanilamide, 323 for Chloromycetin, 334 for penicillin, 579 for streptomycin and about 200,000 for γ-globulin. I should like to make a plea for thinking of these drugs in terms of molarity rather than in μg. per ml. or mg.%.

(5) The outstanding fact about isoniazid is its remarkable specificity. We are engaged in studying its mode of action and hope that information derived from studies of the effect of isoniazid and of synergistic and antagonistic substances will give information about the exact biochemical lesion which it induces and so perhaps lead to the development of even more effective drugs.

REFERENCES

BEYERINCK, M. W. (1889) *Arch. néerl. Sci.*, **23**, 367.
GOULDING, R., KING, M. B., KNOX, R., and ROBSON, J. M. (1952) *Lancet*, ii, 69.
——, and ROBSON, J. M. (1952) *Lancet*, ii, 849.
KING, M. B., KNOX, R., and WOODROFFE, R. C. (1953) *Lancet*, i, 573.
KNOX, R., KING, M. B., and WOODROFFE, R. C. (1952) *Lancet*, ii, 854.
PONTECORVO, G. (1949) *J. gen. Microbiol.*, **3**, 122.

Experimental Investigations in Intracorneal Infections

Professor J. M. Robson said that he would restrict his communication to the use of corneal methods in the investigation of isoniazid given either alone or in combination with other drugs. The investigation described proved particularly interesting as it was proceeding at the same time as the clinical trials, the results being obtained rather more quickly than those of clinical experiments. It was thus possible to see to what extent the results obtained in animal experiments were, in fact, valid in man.

Professor Robson then gave a short description of the rabbit and mouse intra-corneal methods. He then continued: In both cases the organisms are injected actually into the cornea. In the case of the mouse the lesion develops to a maximum in about thirty days and then regresses somewhat. There is never any breakdown nor is there any systematic dissemination in the mouse and hence the animals are always safe to handle. In the rabbit the lesion is progressive, involving the whole of the cornea and spreading into the animal which ultimately dies from generalized tuberculosis. In both animals drugs can be given systematically either in the food or by injection; in addition, in the rabbit the drug can be injected into the vitreous, where a depot is formed; if both eyes are inoculated each animal can serve as its own control.

Results in Mice

Isoniazid produces complete inhibition of corneal tuberculosis during the period of treatment, but after cessation of treatment lesions appear which become as extensive as in untreated animals. This result is similar to the one previously obtained with thiosemicarbazone and different from that obtained with streptomycin where there is some breakdown during treatment, but where protection also exists after cessation of treatment. Isoniazid in combination with streptomycin produces very striking effects; not only is there control during the period of treatment, but very little breakdown occurs after cessation of treatment. These results are in agreement with those obtained clinically.

When isoniazid is combined with PAS the results are no better than those obtained with isoniazid alone, i.e. there is severe breakdown after cessation of treatment.

Results in Rabbits

These are in rather striking contrast to those obtained in mice since treatment with isoniazid not only controlled the infection during the period of treatment, but there was no breakdown whatever after cessation of treatment. In contrast to this streptomycin produced only partial inhibition.

It is not clear why isoniazid should be so much more effective in the rabbit than in the mouse, particularly since the rabbit is *less* resistant to tuberculosis than the mouse. It has been found that the body temperature of the rabbit is several degrees higher than that of the mouse and this also applies to the corneal temperature in both species. It is possible that isoniazid is more effective at the higher temperature, and this question is being further investigated.

All this work has been carried out in collaboration with Dr. R. Goulding.

Dr. D. A. Mitchison:

Isoniazid Resistance In Vitro *and* In Vivo

There are two techniques which have been widely used for testing the sensitivity of tubercle bacilli to chemotherapeutic agents. In one of these a culture on egg medium is obtained from sputum and the growth is then subcultured in Dubos Tween-albumin medium. The test is performed by inoculating from the Dubos medium into tubes of the same medium containing a range of drug concentrations. This method was found unsatisfactory with isonizaid since during subculture in Dubos medium 10 out of 16 strains were found to show a marked fall in the apparent degree of resistance (Mitchison, 1953).

In the second technique part of the primary growth on egg medium is ground up with distilled water and a 3 mm. loopful of the resulting opalescent suspension is inoculated directly on to Löwenstein-Jensen slopes containing 0, 0·2, 1, 5, 10 and 50 µg. per ml. isoniazid (Medical Research Council, 1952, 1953). This method is recommended for routine use. Dilution of the inoculum by 10- to 100-fold, storage of the culture at 37°, and subculture on Löwenstein-Jensen slopes, all tended to cause a fall in the apparent degree of resistance (Mitchison, 1953), so that one should test primary cultures as soon as they become positive and the inoculum should be approximately equal in opacity to that of a ten-day Dubos culture.

Sensitive strains of tubercle bacilli were inhibited by 0·2 µg. per ml. isoniazid in Löwenstein-Jensen medium. When guinea-pigs and mice were infected with strains growing on 0·2 µg. per ml. but not on 1 µg. per ml., treatment with isoniazid at 20 mg. per kg. per day prevented the development of tuberculosis completely or in part (Barnet, Bushby and Mitchison, 1953*a*). However, when these animals were infected with strains growing on 1 µg. per ml. or more the course of their experimental tuberculosis was not altered by treatment at the same dose level (Barnet, Bushby and Mitchison, 1953*b*). Thus there seems some justification for the view taken in the Medical Research Council (1952) that only strains capable of growth on 1 µg. per ml. should be classified as definitely resistant.

REFERENCES

BARNET, M., BUSHBY, S. R. M., and MITCHISON, D. A. (1953*a*) *Lancet*, i, 314.
——, ——, —— (1953*b*) *Brit. J. exp. Path.* In press.
Medical Research Council (1952) *Brit. med. J.*, ii, 735.
—— (1953) *Lancet*. In press.
MITCHISON (1953) *J. clin. Path.*, **6**, 118.

Dr. R. J. W. Rees:

Antituberculous Activity of Certain Non-ionic Detergents

To date, successful chemotherapy of tuberculosis has depended, ultimately, on a direct action of the drug against the tubercle bacillus, a line of approach that has been so successful, in recent years, against the more acute bacterial infections. Yet the natural development of a tuberculous infection is dependent on a much more complicated host-parasite inter-relationship than any of the acute infections. It is therefore surely more than idle speculation to suggest weighting the chemotherapy of tuberculosis towards enhancing the host defence mechanism rather than directly damaging the parasite. This possibility is strengthened by the successful use of calciferol in lupus vulgaris, where certainly the drug has no direct action against the tubercle bacillus, but may well enhance the specific cellular reaction to it. With these ideas in mind I shall outline the experimental results obtained with a non-ionic detergent.

This work started when we found, quite by chance, that a commercial non-ionic detergent Triton A20 produced a striking suppressive effect on the course of an acute tuberculous infection in the mouse (Cornforth, Hart, Rees and Stock, 1951). It soon became apparent we were not dealing with a "chemotherapeutic" agent in the normally accepted meaning of the term, for it did not inhibit the growth of tubercle bacilli in the test tube; it, in fact, promoted dispersed growth in the depth of a fluid medium. Moreover, it was novel to have a non-ionic detergent, highly surface active, with antituberculous properties.

Our chemical colleagues Drs. Cornforth and Stock synthesized an homologous series of non-ionic detergents having the general formula shown in Fig. 1, very similar in structure to Triton A20, some

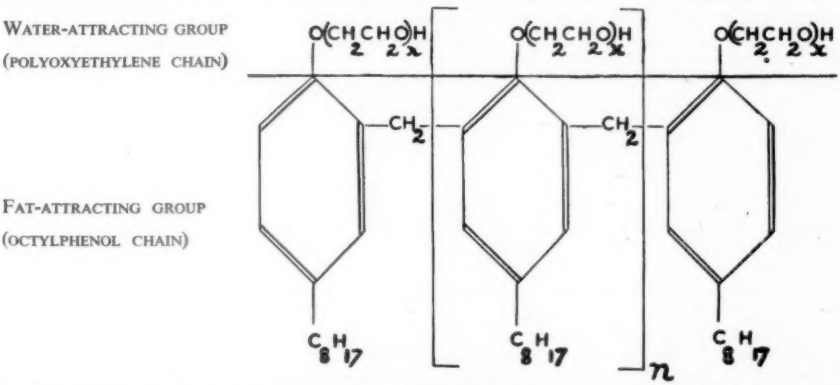


FIG. 1.—Chemical structure of detergents. In the chemotherapeutically active mixture, D2, n = 0, 1, 2, 3 and higher; x = 20 (average value).

of which show similar anti-tuberculous activity but are less toxic than the commercial product. This series is made up of a number of similar units bridged by methylene groups. Each unit has a phenolic nucleus with a hydrocarbon substituent in the *para* position to the phenolic-OH, and this alkyl-substituted phenol (octyl phenol) constitutes the hydrophobic portion of the unit. The hydrophilic portion consists of a chain of predetermined length formed by polymerization of ethylene oxide molecules. The balance of the water-attracting and the water-repellent groups of the molecule accounts, of course, for its surface-active properties. I shall confine my observations, in general, to the chemotherapeutically active mixture, D2 (where n = 0, 1, 2, &c.; x = average of 20).

Chemotherapeutic Tests

These tests have, in general, been done using a standardized mouse test, a test that is now considered reliable for a preliminary assessment. The mice are infected intravenously with a virulent strain of human tubercle bacilli, H37Rv.

The mixture, D2, produced marked prolongation of life, and the degree of protection is comparable to that obtained with streptomycin. While we normally give four intravenous injections on the first, fourth, eighth and eleventh days after infection, a single injection one day, or even five days after infection gives as good therapeutic results. It should be remembered that the recognized antituberculous drugs, like streptomycin, are administered daily. While we use the intravenous route of therapy as the most effective routine test, the subcutaneous and intraperitoneal routes are also effective whereas feeding gives no protection.

The results with D2 in the mouse test indicated the drug had marked activity, and was therefore worth testing in the guinea-pig. A guinea-pig test is considered a more exacting test, and one that can, by manipulation, be used not only to assess protection against a progressive infection but healing or regression of the established disease. In the guinea-pig test the infection was allowed to develop three weeks before treatment was started. The group of guinea-pigs on D2 was compared with streptomycin treated and untreated groups. Treatment was continued daily for sixty days and both drugs, this time, were given subcutaneously.

The streptomycin and detergent treated groups showed marked protection as compared with the untreated group and there was macroscopic and microscopic evidence of regression and healing. While the order of activity of the two drugs was similar, there was probably more residual active tuberculosis in the group on detergent than on streptomycin.

In contrast with the marked activity of D2 against tuberculosis in the adult animal it was found inactive when given to chick embryos infected with tubercle bacilli. It was equally inactive whether administered to the yolk sac, allantoic cavity or intravenously.

(We are indebted to Mr. G. E. Davies of Imperial Chemical (Pharmaceuticals) Ltd., for the chick embryo tests.)

Toxicity Tests

Acute intravenous toxicity tests with D2, showed that doses up to 75 mg. produced no immediate ill-effects. Chronic toxicity tests, on the other hand, all showed liver damage consisting of focal areas of cellular necrosis very variable in extent and distribution but unfortunately uniform. This can be produced by repeated dosing in mice and was present in the guinea-pigs referred to previously. It should therefore be stressed that the therapeutic dose level produces liver damage.

Blood levels.—Present rather insensitive methods for estimating the detergents have shown, none the less, that the drug remains in the blood stream for many hours, even days. No detergent has been found in the blood of mice after massive doses by mouth.

Blood and adrenal glands.—Large doses of the detergent given intravenously produce a marked lipæmia associated with 4–5 fold increase in the cholesterol level in the mouse, guinea-pig and rat. One other very interesting effect was that observed in the mouse adrenal gland following large doses intravenously. The glands were pale pink instead of the normal yellow colour. Such glands when stained with Scharlach R show the cortex to be completely stripped of lipoids and histochemical tests showed no detectable cholesterol in the cortex. A similar depletion of cholesterol and fat was found in the corpora lutea of mice after treatment with D2.

Discussion of the Possible Mechanism

These very promising *in vivo* results in the standard mouse and guinea-pig tests were obtained with a product that has little or no *in vitro* activity against the tubercle bacillus. The only direct effect of D2 on the tubercle bacillus that we have found is the physical one of facilitating its submerged and dispersed growth. But even dispersion in the test tube is not correlated with activity against tuberculosis in the body, since inactive as well as active members of our series can produce excellent dispersed growth. It follows that had these substances been submitted to routine screening of antituberculous drugs *in vitro* before animal tests, they would have been passed over, or rather classed as growth promoters. We are not even sure that surface activity is an essential. Certainly some of the inactive members of the series are as surface active as the chemotherapeutically active mixture D2, and, in fact, differ only from it in molecular size. On the other hand, lengthening the

ethylene oxide chain length of D2, which decreases the surface activity, completely abolishes the antituberculous effect.

It is possible that the detergent although inactive *in vitro* was broken down in the body to produce a chemotherapeutically active compound. Many samples of blood were therefore taken from guinea-pigs and mice, following large and repeated doses, and these were used to culture tubercle bacilli seeded on to glass slides, using a modified Pryce technique, but no inhibitory substance has been detected. This failure to find evidence of an active derivative in the blood does not, however, completely rule out the possibility that such a compound is slowly produced locally or remains intracellular.

Although not bacteriostatic or bactericidal, the drug might decrease the ability of the organism to invade, that is, decrease its virulence. Tubercle bacilli were therefore grown in medium containing the detergent for many generations before being used to infect mice. All such tests show these organisms to be at least as virulent as the parent strain, probably even more virulent. Mice infected with these organisms grown in detergent could also be protected by treatment with the same detergent, showing that growth in the drug had not made the organisms resistant to specific chemotherapy.

It is this lack of demonstrable direct activity on the tubercle bacilli that has naturally stimulated us to consider that the surface-active substance may act primarily on the host defence mechanism. Since doses lower than those required to produce lipæmia, cholesterolæmia or changes in the adrenal cortex or ovary, referred to earlier, are chemotherapeutically active, we consider these changes are probably not essential. The effect of these detergents on the phagocytic activity of macrophages and polymorphs have given no clear-cut positive results.

The only hint of action on the host is the depression of tuberculin hypersensitivity in guinea-pigs treated with D2, first noticed in the guinea-pig test mentioned previously. This phenomenon has now been studied in greater detail using BCG-sensitized guinea-pigs and carrying out quantitative tuberculin tests in detergent treated and untreated groups of guinea-pigs (Hart, Long and Rees, 1952). Such tests show that the chemotherapeutically active representatives of the series diminish tuberculin sensitivity whereas inactive members fail to do so. The degree of desensitization is comparable to that of cortisone, but the mode of action is different. Whether there is a causal connexion between desensitization and chemotherapeutic activity remains as yet unproven.

Conclusion

D2 possesses sufficient liver toxicity to exclude its use in man. New methods are being used to fractionate D2 into more active and/or less toxic products. Undoubtedly we are dealing with a new type of anti-tuberculous agent, and the elucidation of its mode of action, which appears to be through the host, might throw new light on the host-parasite relationship in tuberculosis.

REFERENCES

CORNFORTH, J. W., HART, P. D'ARCY, REES, R. J. W., and STOCK, J. A. (1951) *Nature, Lond.*, **168**, 150.
HART, P. D'ARCY, LONG, D. A., and REES, R. J. W. (1952) *Brit. med. J.*, i, 680.

Dr. P. D'Arcy Hart: We have had many interesting contributions and I shall try to sum up their essential content as they appear to me. An outstanding trend is the conception that in tuberculosis the conditions are much more complex than a directly anti-bacterial agent behaving *in vivo* rather like *in vitro*, but that it is possible to tackle this complexity. Accordingly we have had a series of papers on the relationship : tubercle bacillus–body–drugs.

The elegant corneal technique described by Robson, while primarily useful for defining the characteristics (e.g. the duration) of the anti-tuberculous effects of different drugs alone and in combination, is also clearly a method for studying the natural history of tuberculosis on, in and with the eye. The superior effectiveness of streptomycin plus isoniazid has been well shown. This and other methods and observations are throwing light on the mechanisms of *direct* chemotherapeutic action. But we now have a case, provided by our own work at the National Institute for Medical Research, and described by Rees, which offers a challenge to any technique to explain its mechanism. For these anti-tuberculous surface-active agents appear to be innocuous to the bacillus *in vitro*, and their powerful anti-tuberculous effect would appear to be via the host—so far, however, we have obtained no definite clue as to how. Apart from calciferol on the peculiar condition of lupus vulgaris, this is, we believe, a novel case, but we have only to think of cortisone to remember how in recent years the notion of host susceptibility in tuberculosis has been strongly revived.

Another main trend in this discussion is provided by the contributions of Knox and of Mitchison, which remind us that in spite of the limitations of purely *in vitro* work, there is much to be learnt. This is shown, for example, by Knox's observations on the mechanism of the shifting end-point of inhibition of tubercle bacilli by isoniazid alone, on the effects of combination with streptomycin or PAS, and on the possible use of plate cultures of *M. smegmatis* as a clinical guide. For maximum usefulness of *in vitro* observations, a prerequisite is the standardization of techniques, as, for example,

in sensitivity tests; this has been shown very clearly by Mitchison's work using material obtained by his bacteriological reference laboratory for the M.R.C. trials. His correlations, moreover, of the level of *in vitro* resistance of tubercle bacilli to isoniazid with *in vivo* experimental efficacy of this drug may be of great practical value. They stress the necessity of everyone meaning the same thing when they give detailed reports of *in vitro* resistance.

In conclusion, I carry away three general ideas. One is that each new drug brings with it its special problems and patterns, from a study of which we can get something fundamentally new. The second is that with the revival of interest in the importance of the host in anti-tuberculosis chemotherapy we have turned full circle; for *before* the period following the introduction of penicillin, streptomycin and other antibiotics and the consequent tendency to simplification of the issue as a fight between drug and bacterium, most of us used to think almost exclusively in terms of the host, though in a vague sort of way—rest, sunlight, food, cod-liver oil and even gold therapy. The third idea follows from this rational revival and planned approach to chemotherapeutic needs: Is it too much to hope that some of the anti-tuberculous remedies of the future will result therefrom—tailormade, so to speak, to the body's requirements, instead of off-the-shelf from the empirical emporium?

Contribution by the late **Dr. Marc Daniels** and **Dr. Wallace Fox**

Dr. Wallace Fox: The Medical Research Council's Tuberculosis Research Unit is at present co-ordinating a large-scale trial of isoniazid in pulmonary tuberculosis and analysing the results on behalf of the Tuberculosis Chemotherapy Trials Committee. The trial is being undertaken in 45 hospitals in 14 regions of England, Scotland and Wales, and a large number of clinicians, bacteriologists and pathologists are co-operating. Over 900 patients have already been admitted to the trial, and 400 of them have completed the required six months of observation.

Patients are admitted in three main disease groups—Group 1, acute rapidly progressive disease of recent onset; Group 2, other disease expected to respond to chemotherapy; and Group 3, disease expected to make only a limited response to chemotherapy. Cases intended for Group 1 are referred to a central panel of clinicians and, if accepted, admission to hospital is arranged within a fortnight. Patients for Groups 2 and 3 are mainly selected by the co-operating physicians from patients already under their care.

In order to be eligible for the trial a patient must be bacteriologically positive, as far as is known must not have drug-resistant organisms, and must have had no recent anti-tuberculosis chemotherapy. After acceptance, treatment is allocated from random selection lists, which are held confidentially by the Tuberculosis Research Unit. The treatment is prescribed for the first three months for patients in Groups 1 and 2 and for the whole six months for those in Group 3.

For each patient, progress reports are received after each of the first three months, and a final progress report and case summary at six months. The main items from these reports are recorded on special cards, one for each patient. The data are accumulated, and regular analyses of results are carried out.

The main differences between the present trial and the previous M.R.C. Chemotherapy trials are the rapid admission of a large number of cases, and the continual analysis of the data. There have been several important consequences: (1) The relative effectiveness of the different treatments can be closely followed; (2) results can be reported rapidly—an important point when conflicting claims on the efficacy of a treatment have been made; (3) a close liaison can be maintained with the clinicians since they can be kept informed of the current standing of the different treatments; (4) by taking advantage of the information that the trial itself yields, it is possible to stop the allocation of some treatments and to introduce others during the actual course of the trial. Thus, when the present trial began, the two main treatments allocated were streptomycin 1 gramme daily with PAS 20 grammes daily, and isoniazid 200 mg. daily. When it was found that bacterial resistance to isoniazid alone was occurring, a third treatment, streptomycin 1 gramme daily with isoniazid 200 mg. daily, was introduced into all three disease groups. When the importance and frequency of isoniazid resistance became apparent, the trial was again modified and the allocation of streptomycin with PAS, and of isoniazid alone was stopped completely. At present, a study is being made of the use of isoniazid 200 mg. daily in combination with one of 2 different dosages of streptomycin or one of 2 dosages of sodium PAS. This flexibility in the present trial is a definite advantage since it ensures that the available clinical material shall yield information as quickly as possible.

In conclusion, the present comparative trial demonstrates that a co-operative effort by a large number of clinicians and bacteriologists is a reliable and also a speedy method of answering the problems presented by a new form of anti-tuberculosis chemotherapy.

Professor J. W. Crofton: At the present time there are three main drugs available for the treatment of pulmonary tuberculosis, streptomycin, sodium para-aminosalicylate (PAS), and isoniazid, with terramycin as a possible accessory. The value of these drugs depends on the results of treatment, the emergence of drug resistance and the toxicity of the drug. The results of treatment are being considered by other speakers.

Drug Resistance

Streptomycin resistance.—It is well known that if patients are treated with streptomycin alone, resistant organisms emerge in a high proportion of patients. When a daily dose of 5 to 12 grammes of PAS is given together with streptomycin 1 gramme, the incidence of streptomycin resistance is reduced to 20–30% after three to four months' treatment (Tucker, 1949; Daniels and Bradford Hill, 1952), and if the daily dose of PAS is raised to 20 grammes streptomycin-resistant organisms are found in only 5 to 10% (Daniels and Bradford Hill, 1952). The incidence of streptomycin resistance can be further reduced by giving streptomycin twice a week but daily PAS remains essential. Preliminary evidence suggests that the use of isoniazid with streptomycin may effect an important reduction in the incidence of streptomycin resistance (Medical Research Council, 1952). Terramycin also, in a dose of 5 grammes a day, has recently been shown greatly to reduce the incidence of streptomycin-resistant organisms (Miller *et al.*, 1952).

PAS resistance.—A summary of some reports of the incidence of PAS resistance is given in Table I. Even when a patient's tubercle bacilli have become PAS resistant the clinical significance

TABLE I.—THE INCIDENCE OF RESISTANT TUBERCLE BACILLI IN CASES OF PULMONARY TUBERCULOSIS TREATED WITH PAS ALONE

Author	Total cases	Number resistant	Time of treatment	Dose of PAS per day grammes
Carstensen (1950)	79	10	> 184 days	10–18
Eastlake and Barach (1949)	?	3	(210–1,000 grammes)	?
Delaude *et al.* (1949)	5	5	> 156 days	>10
Medical Research Council (1950) ..	37	12	84 days	20
Véran *et al.* (1950)	20	15	56–182 days	20–30

has been doubted, but if, later, streptomycin is given with PAS to the same patient streptomycin-resistant tubercle bacilli are probably as likely to emerge as if streptomycin were given alone. PAS should therefore never be given alone. There is a great reduction in the incidence of PAS resistance if streptomycin is given at the same time (Medical Research Council, 1950; Veterans Administration, 1951).

Isoniazid resistance.—The preliminary report of the Medical Research Council (Medical Research Council, 1952) has shown that, when isoniazid is given alone, resistant bacilli are found in 11% of positive cultures after one month's treatment, 52% after two months' and 71% after three months'. There has also been a clear indication that patients whose organisms become resistant do less well. Preliminary evidence suggests that the incidence may be reduced by using streptomycin at the same time.

Terramycin resistance.—The available evidence suggests that terramycin resistance will not be very important (Tempel, 1952).

Toxicity

Streptomycin toxicity.—There is a significant reduction in the number of painful injections if streptomycin sulphate is substituted for the more usual calcium chloride complex (McLeod and Somner, 1952). Vestibular disturbances are much less common using 1 gramme a day (20–30%) than using 2 grammes (60–80%) (Tucker, 1949). There is further reduction to about 5% when streptomycin is given two or three times a week (Tempel *et al.*, 1951), and there is some evidence that the incidence may be lowered by giving antihistamine drugs prophylactically (Bignall *et al.*, 1951). Deafness is a negligible danger with streptomycin except when given intrathecally. But it is a real danger with dihydrostreptomycin, a danger which is greatly increased if the drug is used intrathecally (Shane and Laurie, 1950; van Goidsenhoven and Stevens, 1950; Bernard *et al.*, 1950; O'Connor *et al.*, 1951). This risk outweighs the advantage of decreased vestibular damage and, in my view, dihydrostreptomycin should not be used except in some rare case of hypersensitivity to streptomycin in which desensitization has proved impossible and in which there is no cross-sensitivity to dihydrostreptomycin.

Hypersensitivity to streptomycin and PAS.—Hypersensitivity to either of these drugs is similar in its common manifestations and in its treatment. Fever, with or without a rash, is the most frequent reaction and commonly occurs within three weeks of starting treatment. Treatment should be stopped and, when the reaction has subsided, hypersensitivity should be tested by giving successively a half dose of each drug. Rash or fever occurs within an hour or two if the patient is hypersensitive. He may react to both drugs. Desensitization is usually effected without difficulty by giving a small initial dose, 0·1 gramme in the case of streptomycin or 0·5 gramme in the case of PAS, and increasing this daily over two to three weeks.

PAS toxicity.—Nausea, vomiting or diarrhœa are the commonest effects, and the incidence increases with increase in the dose. Nausea can often be overcome by increasing the dose slowly or by taking the drug towards the end of a meal. The more one assumes that there will be no trouble the less trouble there is. Special preparations of PAS, designed to avoid gastro-intestinal upset, should be

used with caution; in at least one of these we have found substantially reduced absorption of the drug. Jaundice is an occasional manifestation and is probably a hypersensitivity reaction; in most reported cases it has occurred after neglect of a warning fever. PAS has an antithyroid action similar to thiouracil and goitre may occur after prolonged administration. I have had two recent cases after some six months' administration. In both radio-iodine tests (Dr. J. A. Strong) have demonstrated the blocking of the thyroid's uptake of iodine, though neither had any lowering of basal metabolic rate; presumably the hypertrophied thyroid was succeeding in manufacturing adequate hormone. In one patient the enlarged thyroid returned to normal within a fortnight of stopping the drug, in the other the goitre disappeared after some three weeks of thyroid administration, in spite of continuing with PAS. Weakness and cardiac irregularities, associated with a low serum potassium, have been reported following the use of PAS (Cayley, 1950; Heard *et al.*, 1950). It is thought that, in most cases at any rate, this is due to liquorice used as a flavouring agent (Strong, 1951).

Toxicity of isoniazid.—Drowsiness, insomnia, tremors of the legs, disturbances of the bowels and bladder, exaggerated deep reflexes and extensor plantar responses have been reported in patients taking isoniazid. In many cases the symptoms may have been iatrogenic and, on doses of 200 mg. a day or 3 mg. per kg. body-weight, no significant toxic effects have been noted in current trials. But if doses of 6 to 10 mg. per kg. are given it does seem that symptoms of peripheral neuritis, or even of mental upset, may occur (Linton *et al.*, 1952). The lower dose, which is highly effective clinically, is therefore to be recommended.

Toxicity of terramycin.—The main toxic effects of terramycin are gastro-intestinal. These were frequent in the patients of Miller *et al.* (1952), who were treated with doses of 5 grammes a day.

The Use of the Different Chemotherapeutic Regimes in Pulmonary Tuberculosis

Many combinations of drugs, and many different dosages and rhythms of dosage, are now available. Some of these are summarized in Table II, in which regimes on which satisfactory evidence is available are printed in italics.

TABLE II.—POSSIBLE CHEMOTHERAPEUTIC REGIMES IN PULMONARY TUBERCULOSIS

I. *Drugs Alone:*
   (1) Streptomycin alone: *Contra-indicated.*
   (2) PAS alone: *Contra-indicated.*
   (3) Izoniazid alone: *Contra-indicated.*

II. *Streptomycin and PAS:*
   (1) *Streptomycin 1 gramme daily with PAS 20 grammes daily:* Of proved effectiveness. Great reduction in incidence of tubercle bacilli resistant to either drug.
   (2) *Streptomycin 1 gramme two or three times a week with PAS 20 grammes daily:* As effective, or almost as effective, as II (1). Probable further reduction in incidence of streptomycin resistance and of streptomycin toxicity.

III. *Streptomycin and Isoniazid:*
   (1) *Streptomycin 1 gramme daily with isoniazid 200 mg. daily:* Very effective. Possibly low incidence of resistance to either drug.
   (2) Streptomycin 1 gramme two or three times a week with isoniazid 200 mg. daily: Probably effective but incidence of isoniazid resistance not yet known.

IV. *PAS with Isoniazid:*
   (1) PAS 20 grammes daily with isoniazid 200 mg. daily: Under trial.
   (2) PAS 10 grammes daily with isoniazid 200 mg. daily: Under trial.
   (3) PAS 10–20 grammes daily with isoniazid 200 mg. twice a week: A possible regime if PAS does not prove to reduce substantially the incidence of isoniazid resistance when the latter is given daily.

V. *Terramycin with Streptomycin:*
   Terramycin 5 grammes daily with streptomycin 2 grammes every third day: Great reduction in incidence of streptomycin resistance.

VI. *Terramycin and Isoniazid:*
   (1) Terramycin 5 grammes daily with isoniazid 200 mg. daily: Under trial.
   (2) Terramycin 5 grammes daily with isoniazid 200 mg. two or three times a week.

Conclusions

Although streptomycin and isoniazid together may be slightly more effective than streptomycin and PAS, if the bacilli become resistant to one they will probably become resistant to the other and the patient will be deprived of the two most effective drugs. Until we know more both drugs should be given daily. This combination is justifiable if chemotherapy is likely to be the definitive treatment, for instance in cases with mild disease and without cavitation in which resistant organisms are unlikely to emerge. It is also justifiable if the patient is grossly intolerant of PAS, if the organisms

are PAS resistant or if, because of previous treatment with PAS alone, they are likely to be so. More complicated cases are best treated with streptomycin and PAS in the first place, reserving isoniazid in case the organisms become streptomycin-resistant later. In desperately ill patients it may be justifiable to use all three drugs in the first place, but personally I prefer to withdraw isoniazid into reserve as soon as a response has been obtained.

REFERENCES

BERNARD, E., PALEY, P. Y., and ARNAUD, G. (1950) *Bull. Soc. méd. Hôp., Paris*, **66**, 583.
BIGNALL, J. R., CROFTON, J. W., and THOMAS, J. A. B. (1951) *Brit. med. J.*, i, 554.
CAYLEY, F. E. de W. (1950) *Lancet*, i, 447.
CARSTENSEN, B. (1950) *Amer. Rev. Tuberc.*, **61**, 613.
DANIELS, M., and BRADFORD HILL, A. (1952) *Brit. med. J.*, i, 1162.
DELAUDE, A., KARLSON, A. G., CARR, D. T., FELDMAN, W. H., and PFUETZE, K. H. (1949) *Proc. Mayo Clin.*, **24**, 341.
EASTLAKE, C., and BARACH, A. L. (1949) *Dis. Chest*, **16**, 1.
VAN GOIDSENHOVEN, F., and STEVENS, R. (1950) *Schweiz. med. Wschr.*, **80**, 1021.
HEARD, K. H., CAMPBELL, A. H., HURLEY, J. J., and FERGUSON, E. (1950) *Med. J. Aust.*, ii, 606.
LINTON, W. S., RABINOVITZ, E., and OLIE, M. (1952) *S. Afr. med. J.*, **26**, 889.
MCLEOD, J. A., and SOMNER, A. R. (1952) *Tubercle*, **33**, 245.
Medical Research Council (1950) *Brit. med. J.*, ii, 1073.
—— (1952) *Brit. med. J.*, ii, 735.
MILLER, F. L., SANDS, J. H., WALKER, R., DYE, W. E., and TEMPEL, C. W. (1952) *Amer. Rev. Tuberc.*, **66**, 534.
O'CONNOR, J. B., CHRISTIE, F. J., and HOWLETT, K. S. (1951) *Amer. Rev. Tuberc.*, **63**, 312.
SHANE, S. J., and LAURIE, J. H. (1950) *Canad. med. Ass. J.*, **62**, 277.
STRONG, J. A. (1951) *Brit. med. J.*, ii, 998.
TEMPEL, C. W., HUGHES, F. J., Jr., MARDIS, R. E., TOWBIN, M. N., and DYE, W. E. (1951) *Amer. Rev. Tuberc.*, **63**, 295.
—— (1952) *J. Amer. med. Ass.*, **150**, 1165.
TUCKER, W. B. (1949) *Amer. Rev. Tuberc.*, **60**, 715.
VÉRAN, P., RIST, N., BALLET, B., BRUMBACH, F., and TRICHEREAU, R. (1950) *Rév. tuberc.*, **14**, 1186.
Veterans Administration, United States of America (1951) Transactions of the 10th Conference on the Chemotherapy of Tuberculosis, p. 194.

Sir Clement Price Thomas: The evidence which has so far been given, results from carefully controlled and annotated experiments, and I am sure you will not expect a mere surgeon to rise to the heights of a statistical survey, but merely to give some clinical impressions of the use of these agents as they affect the surgical treatment of this disease. There seem to be three main effects achieved by antibiotic therapy, firstly the effect on the general manifestations of the disease, secondly the anatomico-pathological changes within the lesion, and thirdly the effect of the therapy on the endobronchial disease affecting the larger bronchi.

Brief consideration of the three factors is necessary. It is common knowledge that the toxic phenomena of the disease are quickly ameliorated under treatment. It is true to say that the improvement, which hitherto took many months of bed rest and supportive treatment, can now be achieved in as many weeks with antibiotics. It is of equal importance that the group of cases one used to designate as slipping chronics now scarcely exists, for it is exceedingly rare to fail to arrest the downward trend unless the patient's organisms have become resistant to the treatment.

The local changes in the disease are in many cases nothing short of being remarkable. One suspects that these changes have a twofold origin, firstly the effect of treatment on the endobronchial disease in the smaller bronchi, and secondly the direct effect of the agents on the interstitial lesions themselves. The former effect is probably of more direct interest to the surgeon. Surgeons have been called upon, certainly up to recent times, to deal with cavitation which has failed to respond to medical means, for example bed rest and artificial pneumothorax. Basing the argument on the assumption that the majority of cavities persist because of a check valve action in the draining bronchi resulting from tuberculous endobronchitis, one beneficial effect of therapy is to decrease the endobronchial disease and thus allow free bronchial drainage throughout the whole respiratory phase, with a resulting decrease in the size or even closure of the cavity. There is, however, evidence to suggest that stenosis of the affected bronchi may occur, in this way producing either closure of the cavity, or, if the disease itself is not controlled, its exclusion from the remainder of the bronchial tree, leaving behind the stenosis either a blocked cavity or a localized tuberculous bronchiectasis.

The effect of therapy on the larger bronchi is of great importance. We have, in the last five or six years, become increasingly aware of the frequency with which involvement of the larger bronchi occurs in association with cavitated pulmonary tuberculosis. As far as one can judge, this was not of very serious import when we were content only to treat these cases by thoracoplasty, for there was evidence to support the contention that if the cavities were closed by such a procedure, then the endobronchial disease took care of itself.

Be that as it may, when we commenced to use resection for pulmonary tuberculosis, the importance of the state of the bronchus at the time of resection soon became evident. It is true to say that in some

cases, the bronchus at the line of section will heal even when it is the seat of gross disease, but all will agree that the presence of active disease at this site enhances the risk of a bronchial fistula enormously, and no surgeon would willingly or knowingly undertake resection in the presence of active endobronchial disease except there were very cogent reasons for so doing. As with bronchi of smaller degree stenosis of the bronchus sometimes follows treatment, not infrequently quite rapidly and one has heard the remark that the treatment has caused the stenosis. This, of course, is not the case; stenosis will only occur when the bronchial wall, in addition to the mucosa and submucosa, has been involved in the disease and the stenosis results from the healing with fibrosis consequent upon the treatment. We are probably not sufficiently conversant as yet with the anatomical characteristics of these stenoses, or perhaps it is true to say that we are as yet unable to predetermine the type of stenosis which may be present. We do know that some are much more localized than others, and in certain cases the stenosis is the main factor in the patient's condition, the parenchymal lesions being almost negligible. This has tempted me on one occasion to resect the main bronchus and the upper lobe, joining the lower lobe bronchus on to the upper end of the main bronchus; the result of this procedure is still *sub judice*, but is encouraging.

These three main effects have altered the face of surgery for pulmonary tuberculosis in that the severe risk case is now seen much less commonly, and consequently patients submitted to operation are in a much better condition to withstand it. There can also be no doubt that resection of the lung for this disease has now become a commonplace and safe procedure, leading to more and more conservative procedures.

Surgeons heretofore have been very concerned about the amount of streptomycin patients had received before they were presented for surgery, this being based on the fear of resistant strains arising in the patient to be operated upon. We found that apart from resection the complication rate following operation was not minimized if these drugs were used over the operative period, but we also found that these complications when they did arise were quickly and satisfactorily rectified if the organisms remained sensitive to the agents exhibited; hence our desire was to treat these patients who were under treatment with antibiotics early before the risk of resistance could arise.

We have been informed that the combination of streptomycin and isoniazid decreases the risk of the development of resistance to both these substances. This changes the whole outlook of the disease, and a position of affairs will arise, which in fact has already arisen in part, where surgery will resolve itself into what may be loosely termed the surgery of anatomical deformity, resultant upon stenosis of either the larger or the smaller bronchi. Treatment with antibiotics will be carried on not merely for months but for anything up to two and a half years, and the surgeon will then be called in to deal with stenosis of the larger bronchi either by resection or plastic repair, and with stenosis of the smaller bronchi by resection of the area of lung behind the block which has not completely resolved.

It is obvious that this line of treatment carries with it serious economic implications, and it is doubtful whether such a course can be followed in all cases. Economic pressure has all along been the factor which has made for compromise between the ideal and the expedient, and I have no doubt that this will continue to be the case for many years to come.

It is not overstating the case to say that at last we can see ahead some real hope of eventually controlling the problem of pulmonary tuberculosis, even if we cannot eradicate it.

Dr. Honor V. Smith:

Tuberculin in the Treatment of Tuberculous Meningitis and Other Conditions

The intrathecal injection of the Purified Protein Derivative of tuberculin (P.P.D.) in a sensitized subject provokes an acute inflammatory response in the C.S.F. which, without doubt, represents a true, specific, tuberculin reaction of the meninges (Swithinbank *et al.*, 1953). In cases of tuberculous meningitis treated with streptomycin such intrathecal reactions appear to be therapeutic (Smith and Vollum, 1950).

37 proven cases of tuberculous meningitis have now been treated with streptomycin and tuberculin and observed for one year or longer. Since treatment with intrathecal tuberculin is hazardous, and as experience in its use was lacking, these 37 cases were specially selected as having a bad prognosis on streptomycin alone. The evidence that tuberculin has a place in treatment is drawn from the clinical findings, the pathological findings, and from the recovery rate.

Clinical Findings

Excluding those patients who are virtually moribund on admission and in whom it proves impossible even to prolong the natural course of the illness, the commonest time of death on streptomycin alone is during the third and fourth months of treatment (Cairns *et al.*, 1950). In such cases the course of the illness is fairly typical: patients enter a period of deadlock which, after weeks or months, is succeeded by sustained deterioration and death, often with a terminal rise in intracranial pressure.

Once this sustained deterioration begins then the prognosis on streptomycin alone becomes almost hopeless (Cairns and Smith, 1952). Out of 18 cases in which tuberculin was withheld until this sustained deterioration had been clearly demonstrated—and which can therefore be classified as streptomycin failures—in 12, recovery followed the addition of tuberculin to the regime of treatment.

Pathological Findings

These recoveries are ascribed to resolution of the meningeal exudate under the influence of the tuberculin. After unsuccessful treatment with streptomycin the cardinal finding post mortem is a dense collar of tuberculous exudate surrounding the brain-stem (Smith *et al.*, 1948; Daniel, 1949; Cairns and Smith, 1952). By harbouring nests of tubercle bacilli this exudate helps to perpetuate the infection (Cairns, 1949) which, by virtue of its anatomical distribution, gives rise to the common communicating hydrocephalus. There are now several cases in which this hydrocephalus progressed steadily in spite of full treatment with streptomycin, to recede under the action of tuberculin.

The post-mortem findings in those cases in which death occurred after a series of intrathecal tuberculin reactions had been provoked, confirm the conclusion that the exudate had resolved. In fact the tuberculin appears to bring about a profound change in the reactions of the tissues, since where there is residual infection this no longer manifests itself as the familiar dense sheet of exudate, but as discrete tubercle formation.

Recovery Rate

Table I shows the results obtained in this group of 37 selected, unfavourable cases treated with streptomycin and tuberculin, compared with those obtained in unselected cases treated with streptomycin alone. Both series have been broken down according to the clinical condition of the patients when treatment was begun (M.R.C. Report, 1948). In spite of the exclusion of all early, and therefore favourable, cases the results in the "Tuberculin" series are rather better than in the "Streptomycin" series as a whole. Even more direct evidence of the value of tuberculin is provided by the 12 recoveries in those 18 cases classed as streptomycin failures.

TABLE I

	Streptomycin only				Streptomycin + P.P.D.			
Stage of disease	Early	Intermediate	Late	Total	Early	Intermediate	Late	Total
No. of cases	24	33	23	80	0	20	17	37
No. alive	18	17	7	42	0	14	8	22
% survival	75	52	30	52	0	70	51	59

Mode of Action

The resolution of the exudate appears to be related to the actual intrathecal tuberculin reaction itself rather than to any desensitization effect. In those cases in which no reactions were obtained no definite clinical improvement was seen; nor did the autopsy findings differ significantly from those seen after treatment with streptomycin alone. There is now evidence that the focal tuberculin reaction is accompanied by intense hyperæmia and œdema of the tuberculous lesion which presumably increases the access of the antibiotics to the site of infection, and also by liquefaction of caseous material (Ebert and Barclay, 1952). Accordingly the aim of treatment is to produce a series of intrathecal tuberculin reactions as quickly and as safely as possible.

Limitations of the Method

The most serious drawback of this method of treatment is its potential danger: incessant observation and some experience in its use are required if disaster is to be avoided. It demands ample laboratory facilities, as daily cell counts and protein estimations are obligatory. It cannot correct errors in the basic chemotherapy, nor, apparently, has it anything to offer when tuberculin sensitivity has been lost. Above all, it cannot renew the diseased blood vessels nor restore infarcted brain tissue. Early diagnosis is thus more important than ever.

Application of this Method to Other Varieties of Tuberculosis

A certain number of cases of tuberculosis other than meningitis have been treated with streptomycin and PAS and with intramuscular injections of tuberculin given in sufficient amounts to provoke a systemic reaction, and followed for a minimum period of a year. These cases were selected according to the following criteria: (1) the infection was proved to be tuberculous; (2) those expert in the field were satisfied that the prognosis on conventional methods of treatment was very bad (in 2 cases of pulmonary tuberculosis a departure was made from this after confidence in the safety of the method had been gained); (3) the organism was known to be sensitive to streptomycin at the onset of treatment. In spite of this a serious degree of resistance developed in 3 cases.

The results in these cases are presented with the greatest reservation. No claims are made beyond stating that the margin of safety proved very wide: no patient grew worse while on treatment, even in those cases in which streptomycin resistance developed.

Pulmonary Tuberculosis

Thirteen cases of pulmonary tuberculosis have been treated in collaboration with Dr. W. Stobie. With 2 exceptions all had extensive disease with cavitation. *Myco. tuberculosis* was easily identified on direct films of sputum in every case but 2, and in these positive cultures were obtained. Three patients had tuberculosis meningitis and one had amyloid disease in addition to the pulmonary tuberculosis.

Two patients failed to improve. Both had previously been treated with streptomycin and in both cases the organisms developed a considerable degree of resistance to streptomycin while under treatment with tuberculin. In spite of this, the tuberculin reactions did not bring about any deterioration, clinically or radiologically. Four patients showed good clinical and radiological improvement, but as organisms could still be cultured from sputum or laryngeal swabs they are classed as partial failures. The rest all showed satisfactory clinical and radiological improvement and cultures of laryngeal swabs became, and have remained, negative.

Lupus Vulgaris

6 cases of lupus vulgaris were treated in collaboration with Dr. Alice Carleton. The length of history varied between 8 and 22 years. Calciferol had been given in every case and 2 patients had received streptomycin as well.

Treatment was limited to a six-weeks course. In all cases the lesions were clinically healed three months after treatment was concluded, though 3 have since showed small areas of reactivation.

Renal Tuberculosis

One case of renal tuberculosis has been treated in collaboration with Mr. Elliott-Smith. Nephrectomy had been performed five years previously and the patient was readmitted with the urine loaded with pus, blood and albumen. Tubercle bacilli were isolated on culture. Intravenous pyelography showed poor concentration in the remaining kidney but no gross deformity. The patient was discharged clinically well and with normal urine in May 1950, and has remained well. The urine is still normal.

Conclusions

In view of the evidence here briefly summarized, it is concluded that in the treatment of tuberculous meningitis, tuberculin, when given in sufficient amounts to promote a reaction, potentiates the chemotherapy. Whether it can do so in the treatment of other forms of tuberculosis is not known, but nothing has yet been seen incompatible with this conclusion, and it is accordingly suggested that this method of treatment merits a planned, controlled trial.

REFERENCES

CAIRNS, H. (1949) *Brit. med. J.*, i, 969.
——, and SMITH, H. V. (1952) Modern Practice in Tuberculosis; London, **2**, 374–375.
——, ——, and VOLLUM, R. L. (1950) *J. Amer. med. Ass.*, **144**, 92.
DANIEL, P. M. (1949) *Proc. R. Soc. Med.*, **42**, 169.
EBERT, R. H., and BARCLAY, W. R. (1952) *Ann. intern. Med.*, **37**, 506.
Medical Research Council Report (1948) *Lancet*, i, 582.
SMITH, H. V., and VOLLUM, R. L. (1950) *Lancet*, ii, 275.
——, ——, and CAIRNS, H. (1948) *Lancet*, i, 627.
SWITHINBANK, J., VOLLUM, R. L., and SMITH, H. V. (1953) *J. Path. Bact.*, **65**, 565.

Sir Geoffrey Marshall: The symposium was concluded by Sir Geoffrey Marshall, who emphasized that one of the most important problems in the chemotherapy of tuberculosis was the avoidance of drug resistance. On no account should any one of the antibiotics be used alone, as sooner or later resistant strains of bacilli would develop and then not only would that drug be of no further use to the patient either singly or in combination, but the patient would become a serious menace to the community as a potential source of infection with these resistant organisms. The speaker then continued: We have seen examples of infants infected by streptomycin-resistant tubercle bacilli who have developed tuberculous meningitis and who inevitably died as there was no effective remedy. When we can use these antibiotic drugs without fear of inducing bacterial resistance, we shall be able to employ them freely at an early stage of the disease, when the lesions are of recent origin and before the majority of the small vessels in their neighbourhood have become sclerosed. We shall then be able to kill the infecting agent before it has become inaccessible to drugs in the blood stream, and we shall be able to halt the disease before tissue damage has rendered it chronic.